FDA PUBLIC MEETING

CLINICAL ACCURACY REQUIREMENTS FOR

POINT OF CARE BLOOD GLUCOSE METERS

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P R O C E E D I N G S

DR. HARPER: If everyone could please take your seats, we'd like to get started. So welcome back to all of you who joined us yesterday for the first day of FDA's public meeting on blood glucose meters. Hopefully you've had a chance to think about what was discussed yesterday and come back for more discussion today on anything you might have thought of or some questions you didn't get to ask. Today, we're really looking forward to having additional discussion on liability, tight glycemic control in hospitals, human factors and use of glucose meters by patients, and use of in hospitals at point of care and risk mitigation issues.

So first of all we'd like to start with a very exciting talk by Jack Bierig. Jack Bierig has extensive experience in litigation challenging government action affecting healthcare providers, copyright and trademark cases and FDA matters. He counsels clients on a wide variety of antitrust association law and regulatory issues. He represents, among others, the American Medical Association and the

College of American Pathologists. He will be talking today on liability issues and the use of blood glucose meters. So I'll welcome Jack Bierig. Thank you.

MR. BIERIG: Thank you, Courtney. I'm honored to be exploring with you this morning on this St. Patrick's morning the issue of malpractice for hospitals and healthcare practitioners in the use of blood glucose meters. I should disclose at the outset that my law firm, Sidley Austin, LLP, represents a number of manufacturers of these meters, although I myself have never worked for any of those companies.

I'd like to begin by encapsulating in a single sentence a general statement of malpractice law. There is malpractice liability if three conditions are met. The hospital or practitioner owes a duty to the patient that was negligent in the performance of that duty, and that negligence was the proximate cause of the injury to or death of the patient. Here, the first and third condition are quite straightforward. Hospitals and practitioners have a duty to patients to provide proper equipment and to utilize such equipment properly. Likewise, it

is quite foreseeable that negligence in fulfilling this duty can be the proximate cause of severe injury and even death. False high reading may mask significant hypoglycemia or may prompt excessive insulin administration, leading to coma and possibly death. Conversely, a false low reading can delay the necessary administration of insulin, resulting in hyperglycemia and its consequences. Therefore, I'd like to focus my remarks this morning on the second element.

And here's the question for this morning. What conduct if any with respect to the use of blood glucose meters by a hospital or healthcare practitioner might reasonably be characterized as negligence? Now, before going on to the specifics of blood glucose meters, I'd like to discuss generally how negligence is determined in malpractice cases. In essence, the trier of fact ? usually the jury, sometimes the judge ? measures the challenged conduct against the so-called standard of care and decides whether the conduct satisfies that standard. So how is the standard of care determined?

The approach varies somewhat from state to state. Basically, however, the jury or judge hears the testimony from expert witnesses for both sides. It also considers other relevant authorities. And those would include governing, legal and regulatory requirements, pronouncements by government agencies such as FDA, statements of knowledgeable private organizations such as the American Diabetes Association, practice guidelines issued by professional societies such as the American Association of Clinical Endocrinologists, the manufacture's package insert where a drug or medical device is concerned, and any other sources deemed by the court to be reliable or authoritative.

I'll just digress at this moment to say that because pronouncements by government agencies are relevant to a malpractice consideration, any public health alert or other notice by FDA can have significant implications for a malpracit3 case. Now, where the conduct at issue directly fiolat4esw a specific law or a specific violation, it is held in many jurisdictions to be negligence per se. There's

nothing further to be discussed. In all other cases, where there's not a specific violation of a law or regulation, the trier of fact evaluates all the relevant inputs and determines what a reasonable person or entity in the position of the defendant should have done. That determination constitutes the standard of care.

With that general summary as background, let me move on to the issues raised by the use of point of care blood glucose meters. At the outset, I don't think there's any doubt that use of such meters would as a general matter satisfy the standard of care. It's true that results from meters may not be as precise as results from blood assayed by a laboratory. But absolute precision is not generally required, as you all know, in the measurement of blood glucose. The FDA has traditionally allowed a 20 percent deviation when reference method glucose values are greater than 75 milligrams per deciliter. While this figure can be debated and is often thought to, should be reduced, the 10 to 15 percent range generally seems to pose little clinical problem. Moreover, bedside

meters allow frequent monitoring and rapid reporting, avoid multiple phlebotomies and cost less. For this reason, their use is widely accepted.

Indeed, the 2010 standards of medical care and diabetes, which was published by the American Diabetes

Association and endorsed by the Joint Commission, note as follows: Safe and rational glycemic management relies on the accuracy of blood glucose measurements, using point of care blood glucose measures which have several important limitations. I want to come back quite soon to the last clause there, which is the several important limitations. But for now, given this sort of statement and the wide acceptance of blood glucose meters, the use of such meters without more should not give rise to any sort of malpractice action.

To get a little bit more controversial, I don't believe that it is malpractice to use blood glucose meters in tight glycemic control situations, even though those devices have not been cleared by the FDA for such a use, as long as the use has been

clinically validated. The fact that a drug or device has not been cleared for a particular use, means that the manufacturer cannot market or otherwise promote it in any way for that use. But it does not mean that use of the drug or device for off-label purposes constitutes negligence. In this connection, a 1982 FDA statement on use of approved drugs for unlabeled indications is quite relevant.

Here's what the agency said in 1982. The Food, Drug and Cosmetic Act does not limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or in patient populations that are not included in approved labeling. Such unapproved or more presciently, unlabeled uses, may be appropriate and rational in certain circumstances and may in fact reflect approaches to drug therapy that have been extensively reported in malpractice literature.

Now, this statement was made in the context of drugs, but it applies equally to devices. Thus, use of meters in tight glycemic control situations

should not be regarded as malpractice to the extent that the specific use is supported by peer-reviewed medical literature or by clinical validation by the practitioner.

Let me return now to the statement of the American Diabetes Association to the effect that use of blood glucose meters has quote, "several important limitations." It is the use of the devices without adequate regard for those limitations that will create malpractice liability. And I have identified four such limitations. You may have identified more or less, but

I've identified four. Here they are: interfering substances, system limits, equipment malfunction and patient misidentification. I'm going to address each of these limitations and consider their malpractice implications. First, however, I want to make an important point about blood glucose meters.

To echo and distort the Declaration of Independence, all meters are not created equal. Depending on the chemistry and technology utilized,

each brand of meter is subject to interference by different substances, has different system limits and has other unique characteristics. Thus, the most basic advice that I would give to those responsible for use of blood glucose meters in a hospital is this. Know the limti8atiosn of the meters at your hospitals and make adequate provision for those limitations.

Let me turn now to specific applications of that general advice. Probably the most serious of the limitations on blood glucose meters is the possibility of reporting significantly inaccurate glucose levels as a result of the presence of interfering substances. Of these substances, the most widely publicized is as you know, Maltose, and to a lesser extent Xylose and Galactos. FDA has issued numerous notices and safety alerts warning of problems caused by the presence of non-glucose sugars in the blood for meters and test strips based on ? I'm not going to get this right ? based on glucose dehydrogenase, pyrroloquinoline quino -- I'll just call it GDH-PQQ as everyone else does ? the agency has warned of 13 patient deaths attributable to false readings from GDH-PQQ

technology. These deaths or severe injuries can be caused by the presence of certain immunoglobulins, abatacept and other sugar- creating substances, and in patients receiving peritoneal dialysis solutions containing Icodextrin, among other things.

Notably, the blood glucose meters that have a problem with Maltose or other sugar interference contain warnings, generally very prominent warnings to that effect in their labeling. I understand, moreover, that some manufacturers of these systems offer education for hospital personnel on the limitations of their devices. Thus, the issue of interference by non- glucose sugars should be well-known to lab directors, clinicians and hospital risk managers. In light of the notices and safety alerts issued by FDA on sugar interference, the warnings about such interference in the package inserts and the programs of manufacturers to educate hospitals about such issues, it is highly likely that a death or serious injury attributable to Maltose or other sugar interference would be regarded as the result of malpractice.

It's somewhat surprising to me that I have not uncovered any case in which this issue has been considered or decided. I attribute this to the fact that it's so cut and dry that probably these cases don't even get litigated, they get settled. But the general principle of malpractice law strongly suggests that exposure in this scenario is of major consequence -- I'm behind on my slides -- there's the basic advice I gave you before. Know the limitations of the meters at your hospital and make adequate provision for these limitations. We talked about this. And as I just said, a hospital at which a death of serious injury attributable to Maltose or other sugar interference occurred is likely to be found liable in malpractice.

For this reason, the lesson is clear. It is essential to review the package insert of meters and test strips used at the hospital to determine whether they are GDH-PQQ-based. If they are, hospital staff must be educated that the meters may not be used if the patient is on an immunoglobulin or other drug or biologic that produces Maltose, is receiving abatacept therapy, is receiving a peritoneal dialysis solution

containing Icodextrin, suffers from Galactocemia or otherwise may have abnormal levels of non-glucose sugars in the blood. If there is any doubt, if there is any doubt whatsoever, the lab director or the hospital should contact the manufacturer or otherwise resolve the issue before permitting use of the system on a patient. The importance of this practice cannot be overstated.

Now, FDA is of course, performing a vitally important public health service in warning hospitals, practitioners and patients of the risks of falsely elevated glucose results from GDH-PQQ test strips where non-glucose sugars may be present. But given the significant implications of its statements, the agency must take care to be precise in what it says. One statement that it made, which in my view may have gone a bit far, was contained in a public health notification dated August 13, 2009. In that statement, in that notification, the agency made the following statement, quote: "Avoid using GDH-PQQ glucose test strips in healthcare facilities," end of quote. Having told the world not to use these test

strips in healthcare facilities, it listed categories of patients for whom such strips should never be used and it set forth steps that can be taken to address the risks imposed by non-glucose sugar interference.

Now, the listing of the categories of patients at risk had the recommendation of steps to address the risk are extremely valuable and extremely important. Moreover, in my judgment, they quite properly increase the malpractice exposure of facilities and individuals who ignore those steps. But the advice to quote, "avoid using GDH-PQQ glucose strips in healthcare facilities" as an absolute matter may go too far. It encourages facilities who have made a significant investment in certain kinds of meters to discard those meters at substantial cost, and it puts facilities at malpractice risk if an adverse event were to arise with such strips for reasons unrelated to sugar interference. In my view, while it is extremely important that the agency warn the public, warn practitioners, warn patients about risks, it should be very careful to word its warnings as precisely as possible.

Now, in this connection, I would note that there are other interfering substances that can skew results. These include acetaminophen, oxygen, uric acid, Vitamin C and L-dopa. There may be others but those are the ones I know about. As best as I can determine, FDA has not issued any notices or safety alerts for these or other interfering substances. That's probably because a deviation from accurate results is generally less with these substances than with Maltose. Moreover, I'm not aware of patient deaths associated with false readings from interference by the other substances. Nevertheless, providers should be aware of interference by other substances, particularly for patients on tight glycemic controls.

Manufacturers of blood glucose meters test for interference by a number of anilities. Any identified interfering substance is generally warned of in the package insert. In light of these warnings, a hospital or practitioner that permits use of a meter in a situation warned against in a package insert risks malpractice liability to a patient who is

injured or who dies as a result of incorrect therapy based on a faulty reading. To be sure, failure to follow the warnings on a package insert does not constitute malpractice per se. That occurs only when there is a violation of a specific regulation or statute. But in most jurisdictions, it will constitute strong evidence that the responsible practitioner and the hospital have failed to meet the standard of care. This fact underscores the need of laboratory personnel and hospital risk managers to be familiar with the package inserts of blood glucose meters and to take appropriate steps to guard against interference.

Now, the second important source of potential liability is use of blood glucose meters outside of system limits. It's very important that a hospital know and understand system limits. Although not as widely publicized as non-glucose sugar interference, this issue has received more publicity of late. At the end of last month, a manufacturer recalled 14,000 test strips that led to false low readings in some circumstances. While no injuries

were reported, the recall highlights the fact that the technology has limits.

System limits relate, among other things, to transient temperature, the humidity to which the strips are exposed, storage conditions and strip expiration dates. Most if not all manufacturers build in so- called fail-safes to lock out use of the meters when the strip has been compromised or when conditions are otherwise beyond the system's limits. However, not every product has the same fail-safe feature. Thus, it becomes important to understand the system's limits, and they are generally set forth in the package insert.

No system guards against false readings due to all limits. For example, there can be a problem with so-called open vial, the open vial issue. Once a container or strips is opened, the strips remain good only for a certain period of time, which varies from manufacturer to manufacturer. Use of strips that have been exposed to the air for more than this period of time may result in erroneous readings. So as I say here, it's very important for hospitals to have

policies in place against use of meters, contrary to system limits, and for practitioners to comply with these policies.

Another example of a system limit is the use of meters on patients with hematocrit values outside the manufacturer's specified range. In patients with a low hematocrit value, a meter may report false high glucose levels. Different systems have different capacities to guard against hematocrit distortion. Accordingly, steps should be taken to avoid use of the meters for patients with hematocrit values outside the range specified in the package insert.

Moving to the third of the limitations, blood glucose meters generally, absent an interfering substance or a system limit issue, report results that do not deviate more than 15 percent from the true value. But as we all know, it's a universal truth that machines and systems sometimes malfunction. If a malfunction does occur and results in patient injury, it is quite likely that a malpractice suit will follow. The best way to limit malpractice exposure in this area is to conduct QC in accordance with the

manufacturer's instructions, or in the absence of such instructions, on a daily basis. In making that statement, I'm well aware that glucose testing is a wave testing under CLIA. I'm not sure why, by the way. Thus, federal law does not mandate QC on glucose meters. However, both the Joint Commission and the College of American Pathologists, as part of their respective accreditation programs, require QC in this area.

If a hospital or a practitioner were sued, the Joint Commission and the CAP standards are likely to be put into evidence. Likewise, the package insert will almost certainly be introduced, and there will be testimony on the importance of QC. Thus, despite the wave status of this test under CLIA, malpractice considerations counsel strongly in favor of performing appropriate QC.

The final area of potential malpractice liability relates to patient misidentification. The Institute of Medicine report, To Err is Human, spoke about the incidence of adverse events due to human error. The Joint Commission has required that test

results be noted in the patients' chart and associated with the correct patient. One can readily imagine the malpractice consequences, to say nothing of the human consequences, if insulin administration to patient A were based on patient B's results. Some manufacturers incorporate patient identification into their meters. A few do not. Many problems stemming from point of care testing are the results of human error, not instrument error. It is important, therefore, that a hospital which uses meters without a patient identification feature makes sure that it has a system in place to avoid patient misidentification.

I want to sum up now in two ways. First, I want to say that use of point of care glucose meters is well within the standard of care. Each brand of these meters has limitations, which should be understood and addressed if malpractice risks are to be minimized. Having said, that, I'm now going to recommend ten steps to guard against malpractice liability from the use of blood glucose meters. Given that mosaic number of ten, I'm going to refer to the as the ten commandments of blood glucose. I'm not

going to do it in biblical text, however. I was tempted to do it, but thought it would be a little bit artificial.

Here there are, the ten commandments of blood glucose meter use. For meters that use GDH-PQQ technology, educate staff and patients about the potential for falsely elevated glucose results in the presence of Maltose or other non-glucose sugars. Make sure that the meter is not used on patients who are having therapy or will have a condition that produces non-glucose sugars. For all meters, be aware of the manufacturer's instructions for proper use, storage and handling of strips and meters and have policies in place and enforced to follow those instructions. Three, train all responsible personnel on the proper use of the meters, document the training, and alert all such personnel to relevant FDA pronouncements and any updates or notices issued by the manufacturer. The fourth commandment. As the FDA has advised, consider using drug or action alerts in computer order entry systems, patient profiles, and charts. Fifth, know the hematocrit levels at which the meter

functions effectively. Don't use the meter on patients whose hematocrit levels or outside the specified range. Six, perform QC on each meter as recommended in the package insert, or at least once a day. Seven, as the FDA has also counseled, consider periodic verification of glucose meter result with laboratory-based glucose assays, particularly in tight glycemic control situation. You recall I said that I didn't think it was malpractice to use glucose meters in tight glycemic controls situations, but that was subject to clinical validation, and certainly comparing the results and verifying the results by comparison with laboratory- based glucose-based assays is a very good idea.

The eighth commandment. Implement a system, either through a fail-safe system on the meter or through general hospital protocols to ensure that there are no patient misidentification errors. The ninth commandment. If there is any issue regarding use of a particular meter for a particular patient, don't use the meter until you are satisfied that use on the patient is safe. And the final commandment

really sums it all up and harkens back to the second commandment. Most generally, know the limitations of any meter as set forth in the package insert or as set forth in FDA announcements, and make sure that the use conforms to these limitations. If you harken diligently onto those commandments, I think that patients will get the benefits of point of care blood glucose meters, and manufacturers, hospitals and practitioners will minimize their risk of malpractice liability. Thank you.

MR. BIERIG: I'm hoping ? what Courtney didn't say is I also teach health law and policy at the University of Chicago, so I love getting questions.

DR. HARPER: Yes. We do have a little bit of time for questions, and I'm going to start it off, because I have one or -- maybe it's kind of two questions.

MR. BIERIG: I was getting worried when I saw you taking notes there, Courtney.

DR. HARPER: Well, my question is, it's very clear that where FDA issues of public health

notification or something like that, that that is a clear message to practitioners that it might be malpractice, if that still resulted in a death or serious injury. But what about contraindications and label limitations. I wasn't as clear as that from your talk, and I'll give you an example. Most of the meters that we clear actually limit against using critically ill patients. So I wonder, where you say that where's there's a clear limitation or alert, it would be malpractice but it wouldn't be necessarily be malpractice to use if it it's accepted. Where does that line get drawn?

MR. BIERIG: That's an excellent question. Acting contrary to a package insert, as I said in my presentation, is not in and of itself malpractice. But there's no doubt that a plaintiff's malpractice attorney would introduce the package insert into evidence, would argue that use contrary to the package insert is strong evidence of malpractice, and then it would be up to the defendant to explain why although that is required by FDA, it really does not reflect the standard of care. So there would be expert

testimony to the contrary or medical journal articles to the contrary. But there's no question that the fact that that kind of limitation appears in the package insert would be a very important fact in a malpractice action.

DR. HARPER: Are there any examples about how that's gone one way or the other that are similar?

MR. BIERIG: Not in this context. As I said, I can't find -- I searched and I had two or three other people searching to find cases involving malpractice, reported malpractice decisions in the context of blood glucose meters, and we couldn't find any. And I suspect that's not because there haven't been any, but because when the defendant or the insurance company representing the defendant sees the case, they figure it's best to just pay rather than to litigate. That's my guess.

DR. HARPER: What about for other medical devices? Are there any ?

MR. BIERIG: Yeah, there are cases to that effect.

DR. HARPER: And then the second part, which

you may have answered a little bit, you mentioned -- they said if FDA hasn't released a safety alert on some of the other interferences -- and there have been deaths from dopamine, there have been deaths in critically ill patients, there have been deaths in patients with renal failure. SO I don't know that everyone knows that, because FDA didn't actually do a public alert. Does that impact these types of cases?

MR. BIERIG: Well, the fact that the agency hasn't issued an alert would certainly be used by the defendant in a case like that. Let's say there was L-dopamine interference, and then there was an action against the hospital or a clinician. They would say, we weren't negligent; we had no basis for knowing that that was a problem so of course we didn't check. So the fact that the agency hadn't issued an alert would be a fact. Now, if there's literature out there --

DR. HARPER: It's in the labels.

MR. BIERIG: Or it's in the labeling, personally I would rather be on the plaintiff's side of that case, if it's in the labeling.

DR. HARPER: Well, this is very interesting

to me, because I don't know anything about this area. Thank you.

MR. BIERIG: That shouldn't stop you.

DR. STOREY: Andrew Storey from Cangene. It's a great presentation. I liked your commandments. They should be easier to follow than the other set.

MR. BIERIG: However, unlike other set, they are mutable, so I'll --

DR. STOREY: But I did have to take exception with the first commandment, which is that GDH-PQQ meters should not be used for any patients that are being provided Maltose-containing products. Because there are several licensed Maltose-containing products out there that contain Maltose in such low concentrations that they do not provide any interference with those meters.

MR. BIERIG: I accept that. This may be why Moses had to go up a second time to -- that's a very valid point, and I may -- having criticized the FDA for going too far, I may have been slightly inaccurate myself. I think that's a valid criticism.

DR. STOREY: It really depends on the

concentration of Maltose in the product and the dose of the product.

DR. BIERIG: I accept that, and I should modify that and will.

DR. BEASTON: Patricia Beaston, FDA. How do you describe or define widely published? A lot of times somebody will come out with one big study and then everybody jumps on the bandwagon and they start doing that. But the patients aren't always well-described. The protocol isn't complete, but people start following that recommendation. And as we'll discuss more and was discussed yesterday with tight glycemic control, it seems to be a moving target. So when you want to defend somebody using off-label products, how do you defend that as widely published?

And then the second question is, you speak to hospitals and practitioners, but if you're a practicing physician not in the hospital and you have patients who might be using 30 glucose meters and you have no way of knowing the individual performance characteristics of those meters, what's your liability when you tell your patient to use a glucose meter, and

they may be getting medications from five different physicians?

MR. BIERIG: Okay, let me try to answer both of those. Stand up there; don't go away. How do I define widely publicized? Well, I don't define it. In terms of the defendant, if there are studies out there that the defendant has looked at and considers reliable, that is the basis for a defense that the conduct by that practitioner, that hospital, whoever it is, was not negligent. If there's an article that's published in JAMA or the New England Journal or in a Journal of Clinical Endocrinology, sure, it's subject to debate. That's how science and medicine advance. But if it makes sense, if it seems like it's a ? it's certainly going to be peer-reviewed. If it seems like it's well-controlled, I think that provides a basis for a defense. Remember, at the end of the day, one of the amazing facts about our legal system is, these very complicated medical questions get decided by a jury of people who don't have the foggiest clue of what's going on.

I give a speech on why doctors hate lawyers

-- it's actually excellent. But it's interesting, in medicine when you talk about peer review, you talk about review by other physicians or by other Ph.Ds. That's peer review. In law, when we speak of a jury of one's peers, those peers are truck drivers and elementary school teachers and unemployed people and students. And so these decisions get made by people who really don't understand not only the nuances but even the basics of these issues. So the fact that something has been published is a fact that gets put to the jury and that the jury has to decide. That's my answer to your first question, whether it's satisfying or not, that's my answer.

The answer to your second question is, it's a real problem. Fortunately, my talk today was on liability of hospitals and practitioners at hospitals. But for a practitioner who's seeing as you say in the office, may people who use blood glucose meters and they have very different meters, I think it's probably an extremely good idea for the physician to put out sort of a two-page, one or two-page information sheet for the patient in which the practitioner generally

describes various meters and says, if you have this condition or that condition or the other condition, you might consider not using this meter or using that meter, that might help. Because as you say, you don't know all the medications that you're patient is on, you may not know exactly which meter the person has, they may switch without your knowing. So you're in a difficult bind.

But I think having some kind of patient education material is a good idea. That's not to say if you don't have that that you're necessarily going to be liable in malpractice, but in terms of best serving the patient, I think giving the patient some idea of the kinds of considerations that we're talking about, only in very lay non-technical terms, is probably a good idea. That's my idea.

DR. BEASTON: Thank you.

DR. HARPER: Unfortunately, we don't have addition time right now for questions, but we will bring Jack back up for the Panel discussion later if he's still around.

MR. BIERIG: He will not be around.

DR. HARPER: So you can talk to him at the break.

MR. BIERIG: Okay, you can talk to me at the break. Thank you very much.

DR. HARPER: Thank you. So just one accouchement before we start with Session 3. So anybody who needs to go to the airport later, we actually have a sign-up sheet outside at the registration desk, and you can sign up for taxis to the airport this afternoon. So I encourage you all during the break to go and sign up for times, if you all need to get to the airport.

Now, it's my pleasure to introduce Irl Hirsch, who is the moderator for Session 3, for Tight Glycemic Control. Dr. Hirsch is a professor of medicine and holds the Diabetes and Teaching Chair at the University of Washington School of Medicine, Seattle. He's interested in new technologies for the treatment of diabetes, particularly those involved in insulin therapy. So we welcome Dr. Hirsch.

DR. HIRSCH: Great. Thank you. Thank you very much and welcome to Session 3. Couldn't take

this opportunity without having a few introductory comments before we get started. Want to put an historical overview into where we are as we move into this Session 3. Pre-1980s -- many of you were around then, seen patients. You all remember the topic of fractional urine testing, as I see some heads nodding, and the introduction of sliding scale insulin, which by the way, I could first find mention in in a textbook from the early 1940s in a surgery textbook. And this is what we did. Many of you remember this.

And then the introduction of bedside capillary testing in the 1980s, however, did not change the culture of sliding scale insulin. But until 1987, bedside glucose testing used enzyme-based photonic methods, mostly by measuring change and light reflectance of a dye-containing strip resulting in a glucose oxidation reaction. And today, as you know, almost all finger stick testing is performed with electro chemical methodologies, which allows smaller volume of blood and faster tests.

Furthermore, as we move down this historical overview, there has been little attention to glucose

control in the hospitals until the randomized control trials and retrospective data by some of the people in the room today, including Van den Berge, Furnary, Krinsley, and many others suggested that TGC or tight glucose control, should be the standard of care. And then of course, ADA, AACE, Society of Hospital Medicine and many other societies around the world created standards for in-patient targets, particularly in the ICU.

So what happens. Well, the RCTs for glucose controlled and other settings, such as myocardial infarctions, MICU and sepsis, did not show that tight glucose control improved outcomes. And then last year, we had the announcement of the study NICE-SUGAR, which showed attempts that tight glycemic control may actually worsen outcomes. So while tight glycemic control consistently showed increases in hypoglycemia rates, independent of these studies, new research showed that hypoglycemia results in more severe arrhythmias than we had appreciated, in addition to the fact that hypoglycemia in and of itself led to

inflammation on top of the known CNS side effects. So hypoglycemia, bad.

And then last year in the New York Times there was an article that pointed out that glucose meters in general, including those in the ICUs, are not as accurate compared to the perception on top of the fact that there are important interferences, which we just heard about, noted for many types of meters. And the article that was quoted in that New York Times article actually comes from the CDC, which showed up to a 32 percent variation in blood glucose results.

So the main questions for us now is what is the impact of tight glycemic control if it can be done uniformly in both academic and community hospitals without hypoglycemia? Is it possible to do this with today's bedside glucose technology? And do we need better technology for bedside blood glucose testing? I think these are some of the fundamental questions. And finally, what is the role in the ICU of continuous glucose monitoring, and would tight glucose control efforts improve? I for one think it very well may. These are just some of the devices that are now being

tested for intravascular testing. And again, the question is, will tight glycemic control be possible in most hospitals once this technology is available?

I was provided a list of questions I want you to think about with our speakers and our discussions this morning as we go through this Session 3 about TGC in the hospitals and ICUs, and think about these. First, what is your estimate of the percentage of hospitals that use tight glycemic control in the United States. What factors must be considered as physicians weigh the risks and benefits of using blood glucose monitoring in hospitals settings, and how do we balance this need for faster turnaround with known inaccuracies of meters? What types of issues determine whether a patient will or will not be kept on a tight glycemic control protocol? And how often do users, both in the hospital and at home, actually see or read the labeling so they are familiar with the limitations of these meters? Ms. Hanson will be discussing risk mitigation in hospital settings later, but do you believe hospital staff are trained and certified to ensure they understand these limitations?

And how do thoughts of the liabilities that exist in hospitals influence decisions to follow these TGC protocols? Do the cost or reimbursement for strips themselves affect the way meters are used in hospitals in this country? And finally, what types of reimbursement incentives might be developed by payers, whoever the payer may be, for manufacturers who develop more accurate and reliable blood glucose monitoring systems?

So what we will be doing this morning is looking at various aspects of TGC in the hospital, first from an FDA perspective with Carol Benson, then a payer perspective with Jim Rollins. Then we will be hearing after the break about advantages of tight glycemic control in the hospital by Rich Bergenstal, then why tight glycemic control may not be appropriate by Dieter Mesotten. And finally, I will be talking about current practice and experiences with TGC in hospital settings.

So that's by way of introduction. I would now like to introduce our first speaker, who's going to be talking about regulatory challenges for safe use

of blood glucose meters in hospital settings, will be Carol Benson, who is an Associate Director of the Division of Chemistry and Toxicology Devices in the Office of In Vivo Diagnostic Device Evaluation and Safety. Carol?

DR. BENSON: Thank you. This morning I am going to be talking about the regulatory challenges for the safe use of blood glucose meters in hospital settings. This is an overview of what I'm going to be talking about. First I'm going to be talking about the intended use that the manufacturers seek when they come to FDA for clearance with their blood glucose meters. What are the implications under CLIA for the clearance of blood glucose meters? Whether FDA's acceptance criteria for accuracy. Whether some issues that are specific to the hospital glucose meters and test strips. We look at these as a whole system, not just the meters, but the meters in combination with the test strips. And also, I'm going to be reminding us about the post market issues and what they're telling us.

When manufacturers come to FDA for clearance

for their glucose meters, they seek clearance for marketing for both lay users and for professionals. When we have a clearance for lay users, we consider this an over-the-counter device. So you may be wondering, why do manufacturers seek clearance for both lay users and home users? Well, according to the CLIA regulation, 493.15, all glucose monitoring devices that are cleared by FDA for home use are waived by regulation. So when the manufacturer gets their clearance by FDA, they also get a waived device. They get a CLIA categorization for a waived device.

What are the implications of a CLIA waived device? Well, anybody can use the device in any setting. You get a certificate from the Centers for Medicare and Medicaid Services, and you follow manufacturer's instructions. You need to follow the manufacturer's instructions for testing and for performing external quality control. Now, the manufacturer needs to recommend what type of external quality control to do because under CLIA, there are no requirements to do external quality control for a waive device. And also, there's no requirements to

perform any proficiency testing. And there's no requirements that the personnel need to be trained.

There is a way, though, to obtain a CLIA waive device other than seeking clearance for over-the- counter devices. In 2008, FDA published a guidance here for recommendations for waiver applications for manufacturers of in vitro diagnostic devices. This is on their Web site. These studies, though, are generally more robust than the typical type of studies that are done for lay users for an over-the-counter device. The requirements generally are that 360 samples are tested. We ask that they be tested in a minimum of at least three sites, that the testing be performed by the typical type of people in the waived settings, and that they test this information over time, a minimum of two weeks.

The accuracy criteria for blood glucose monitoring devices under the CLIA waiver studies is tighter than the ISO 15197 standard. Here, we are looking at 95 percent of the results to be within plus or minus 15 percent of the values that are equal or greater to 75, or plus or minus 12 milligrams per

deciliter for values that are under 75. CLIA waiver studies are also, the evaluation is we look at the other 5 percent of the values. The ISO criteria, remember, we don't know what happens to those other 5 percent, but when we wrote the CLIA waiver guidance, we set up some kind of a limits, called limits of erroneous results. And we see, where do those other 5 percent of the results fall.

So we look at these other 5 percent of the results, and we have these limits set up as to where we think, that if results fall in that category, they would be so egregious that they would cause harm to the patient. And in addition, we ask the manufacturers to perform flex studies. These are studies in which the devices are stressed. Tried to find out, what could the user do that could cause an error in the device. Some of the things we learned yesterday, we know that perhaps we can't test for. Like, if somebody leaves the vial strips open, they don't wash their hands. That's not something that they can stress the device to detect. But supposing that the device has an operating temperature. They can

stress the device to see, does the operating temperature they recommend -- I mean, does it fail just one degree past that recommended time or does it fail two digress before that time?

We have regulatory challenges when we clear meters for both over-the-counter for lay users and for healthcare professionals, because many of these meters we know are designed for health professionals only. These meters are rather large, they have docking stations, they have barcode capabilities, they transmit data, they have quality control lockouts, and they have large memory capacity to store data -- all the things that health professionals want. But the manufacturers seek clearance for over-the-counter.

Also, the regulatory challenges for us are that we use the same minimum accuracy criteria for the lay user studies as we do for the healthcare professionals. We learned yesterday that about 100 patients are tested for lay users, and their results are compared to reference methods, such as the YSI. And then the health professionals test 100 patients and their results are compared to the YSI. However,

in these studies when we seek clearance for both, generally the same patients are tested for the studies. The laypersons test first and then the health professionals test the laypersons. These are not being tested on sick hospitalized patients. They don't see that data.

Also, we do use the minimum ISO criteria from the ISO 15197 standard. And I thought about giving us a quiz today, because I think by now we can all say this in our sleep -- that we're looking at 95 percent of the results that need to be within plus or minus 15 milligrams per deciliter for values that are less than 75 or plus or minus 20 percent for things that are greater than 75 milligrams per deciliter.

The use of this criteria, though, brings us regulatory challenges, because we know that there can be large differences between the meter and the reference method. For example, we know that if a value is 60, by the reference method the meter can vary from 45 to 75 and be considered acceptable. If it's 200 on the reference method, the meter may vary as much as 160 to 240 and be acceptable. And only 95

percent of these results need to meet the minimum accuracy criteria. So if 100 are tested, only 95 meet it. What happens to the other 5 results or the other 5 percent? They're not evaluated.

We know that the ISO 15197 standard is written for meters and test strips that are designed for lay users only. Should they be tightened for lay users? We talked about that a lot yesterday. We know that this criteria are broader than the College of American Pathologists requirements for laboratory-based systems, which are 10 percent, or 6 milligrams per deciliter, whichever is greater. But currently, FDA applies this criteria to all meters and test strips, except those that come through for CLIA waivers for studies. Are these too broad for hospital use meters to be safe and effective? That is the question.

We heard also about the problems with interfering substances and that these are cumulative in the patient, hematocrits, drugs that the patient may be on, dopamine, acetaminophen; do they take Vitamin C or they have a high lipid? Has the

temperature of the strips been compromised? Are we at a high altitude place? Do we have humidity? So if each of these affects the glucose by 10 percent and they're evaluated separately, what is the cumulative effect for the patient? Well, if we were to add all these up, I'm not sure we actually know what the cumulative effect is for the patient.

Hospital patients bring challenges, because they're usually sick. They're dehydrated, they may be in shock, be on oxygen, and they probably have different hematocrits from patient to patient. And these hematocrits might not necessarily be known at the time of the testing. Probably are on multiple drugs. We don't know how they affect the system. They may be patients whose glucose values are changing rapidly. And they're tested with multiple meters by multiple users, which introduce error. Therefore, the patients are treated immediately, whereas the lay use person, they test their blood glucose, they have a chance to look at the value, and they can decide if they need to act on that value. Hospitalized patients are tested and treated.

And more importantly, what are the consequences of hospital patients being tested with multiple meters? From this recent article in 2009, we find that hepatitis B virus infections are associated with blood glucose meters, and they're increasing in the United States. And it may be a totally unaware problem. These meters need to be designed so that they can be disinfected multiple times. Hospital patients, according to another arable we know, may also be subjected to insulin dosing errors. If we have a 20 percent total error, we can have greater than 30 percent of the insulin doses can be different from those that were intended, and we might miss a significant number of hypoglycemic events.

The regulatory challenges we face with hospital meters are, what is the intended use once it gets to the hospital? It may be for that which is different from which it's being cleared. It may be being used for tight glycemic control. And what type of accuracy from the meters is needed to achieve that type of intended use? We've heard a lot about the

interferences that could be present in hospital patients -- Maltose, talked about drugs, oxygen, dehydration. They could be in DKA. And there could be a total unawareness of the user of these potential interference or limitations in the labeling.

Currently, the challenges we face with labeling are that the labeling for the healthcare professionals is the same labeling that we use for the laypersons. We add an additional section for healthcare professionals only. And in this we have though the same limitations. And the limitations that we put in for glucose meters are not for use on critically ill patients, those in shock and dehydrated. We put the accuracy criteria of the 15197 standard as it's requested by the tables in that guideline. The one problem with the labeling in hospital systems it that probably the labeling is not right next to the meter. The nurses have a day job. They may not necessarily have read the manual. They may not necessarily understand the limitations of the labeling, and do they know when to test quality control materials? If some of these meters have

quality control lockouts, then they're reminded when to test for quality control.

We believe that for safe and effective use of the hospital meters, that we will need technology improvements. We will need tighter accuracy criteria. We would like to have less interference from drugs and hematocrit and oxygen and altitude and all the things that could be cumulative for the patient, and less lot to lot variability. When devices are submitted to FDA, three lots of test strips are evaluated in the studies. But after the device is on the market, it's up to the manufacturer to have lot release criteria that they monitor. Lockouts are wonderful for quality control. Can they also detect expired reagents? We know that we can't detect people leaving the test strip vials open for longer periods of time than is recommended. And they need to have cleaning procedures that would prevent infections, such as hepatitis.

Yesterday Courtney presented all the information about the post market signals, but I wanted to remind us that many of these signals are

coming from hospital use meters. We have over 12,000 reports. But we also learned that the denominator is very large for glucose use. We have though, 100 deaths that have occurred from 1992 to 2009. But also, Courtney gave you the Web link, because anyone can report problems with glucose meters. Lay users can as well.

In summary, I'd like to say that manufacturers seek clearance for both the lay user and the healthcare professional. And why they do this. Why does the impact of a clear waived device on glucose meters? And that FDA's minimum acceptance criteria are tied to an ISO 15197 standard that's designed for lay users. That hospital meters cause problems because they're used on multiple patients and tested by multiple users. They're also used on patients who could be critically ill. They could be on many drugs, have different hematocrits, and they present infection control issues for us. And our post market signals are telling us that there are some problems with glucose meters, but we know that anyone can report these problems, and we do encourage them to

do so. Thank you for your attention.

DR. HIRSCH: You can step to the microphone and introduce yourself for questions. I guess I have a tiny itsy bitsy question for you. And that is -- and maybe you alluded to this, but the question still remains to me anyway, especially in the hospital, what should the standard be? You showed us what they are now. You showed us the huge variability in glucose levels that meet the standard. Should the standard be changed?

DR. BENSON: I think that's the question that we're dealing with right now. We're asking for, what are appropriate acceptance criteria for use of meters in hospital settings?

DR. HIRSCH: And what is your opinion of that?

DR. BENSON: Well, I think we believe that they need to be tightened.

DR. HIRSCH: Okay. Yes, front microphone.

MS. HERTEL: Yes, Connie Hertel from AgaMatrix. I was wondering if you could comment on labeling of the system kits regarding accuracy; for

example, proven accuracy, high accuracy, et cetera?

DR. BENSON: We don't like to have patients, or manufacturers to infer that their devices are better than another device. Because what we do is we're comparing the performance of that device to a recognized reference standard. The ISO 15197 has a table that is suggestive of how to display the performance. We have included that table in the labeling, but we don't want someone to say that my device is more accurate than another device, or more accurate than what are current standards.

DR. HIRSCH: Next?

DR. HELLMAN: Hi. My name is Richard Hellman. I'm a practicing endocrinologist. The reason why I think you are talking about needing to tighten the standards of accuracy in hospital settings is because of the illness, the severity of illness, and the comorbidity conditions that the patients often have.

But in fact, there are many settings in which there are patients who are very vulnerable: a patient with stage 5 renal failure in dialysis units,

people in intermediate units, people in long-term care, people with multiple comorbid conditions, people who have ketoacidosis or are seen in the doctor's office. Why would not the meter accuracy need to be better for all of those people to protect the patients with a similar comorbid or severity of illness?

DR. BENSON: I think we are asking that accuracy standards be tightened for all glucose meters, for whether they're being used over the counter or they're being used in any healthcare setting.

DR. HELLMAN: I think the goal is to protect the patient, and if the vulnerability of patients suggests an urgency to correct, it would seem that since vulnerable patients are found throughout the system, a more general approach would be appropriate. Thank you.

DR. BENSON: Okay.

DR. PINKOS: Can I ask you a question? Do you believe that the performance requirements should be equally tight for home users as in hospitals?

DR. HELLMAN: That's a very important

question. I think the real problem is actually making that happen. Because the public actually are less knowledgeable about the meters, and the issue of how to properly educate people in their use is really one that we really haven't begun to grasp. But in fact, if the goal is to protect people and the key is getting accurate information, I think there needs to be a way in which we come to grips with the reality that wherever the person is, they need to have something to rely upon. And whether it be a patient with Type 1 diabetes getting into their car ? and you have data on that, as to the high frequency of errors, or others -- I think providing people with something that is accurate, it will save lives. And I think we probably need to grapple with that, even though it's more difficult.

DR. HIRSCH: Next question, please?

DR. SOLDO: Good morning. Monnett Soldo from OptiScan again. Dr. Harper started by saying that perhaps we will think about what we talked about yesterday and come back with some additional thoughts.

Late yesterday I brought up the question of

whether interferences should be considered as part of the accuracy spec itself or not. In other words, should we even be talking about accuracy in the absence of dealing with interferences? And I would argue even more strongly in an ICU setting. We have over 1,400 points from ICU patients, and some of these people are very sick, with multiple system organ failures and sepsis and so on. And from our experience, it would be a rare instance to find something in ICU setting that didn't have a drug on board. And frankly, as much as I would like to consider tightening this spec, it's not obvious to me that people can meet the current spec in the face of those interferences.

So I would argue very strongly that we need to demonstrate that we're actually even meeting the current spec as well as having the discussion on tightening it across the board. I think it's important. If you're not taking into account interferences, then frankly in an ICU setting, I don't know what we're doing.

DR. BENSON: I think we would concur with

you.

DR. HIRSCH: Thank you. Next question, please?

MS. HERTEL: Hi, Connie Hertel again, from AgaMatrix. Again, getting back to the labeling. Since I do the submissions, I'd like a more definitive answer if you don't mind, in that if we do a submission with that type of labeling, will it be told to us to remove it?

DR. BENSON: Yes.

MS. HERTEL: And is that against the whole -- - all manufacturers?

DR. BENSON: We would like to -- we apply that to all manufacturers, because we would be getting into superiority claim wars. So that's why we'd like to use the standard recommended table and how to display accuracy that's from the ISO standard.

DR. HARPER: The data we get do not in any way give anyone the ability to claim that they're more accurate than another meter. Those studies aren't done.

MS. HERTEL: Thank you.

DR. HIRSCH: Last question?

DR. CEMBROWSKI: Under the influence of wine last night, but for laboratorians who evaluate periodically new lots of either Live Scan, reagent, or growth reagent, we thought that it is possible for these manufacturers to manufacture lots that are within plus or minus 12-1/2 percent. So we think -- we would urge the FDA to contemplate this, for hospital patients, the new lots that should be approved, 95 percent of the observations should be within plus or minus 12.5 percent. It is doable, but companies would have to stretch to produce this product.

DR. BENSON: Thank you.

(Pause.)

DR. HARPER: So, we are have having to change laptops for the next presentation, so we have a little bit more time for questions or discussion on this topic or some of the topics we discussed yesterday.

DR. CHRISTENSON: Rob Christenson from University of Maryland. I have a question about

training actually. Dr. Harper yesterday mentioned this issue with GDH and PQQ and sort of asking how maybe we can better communicate, and I think the issue about training for glucose meters in hospitals and all the issues that come up with those. And I wonder if there is an evidence base that shows what practices work well and what practices don't work as well, so that it might give us some guidance as to how we can best go about those things. There's an effort now at the CDC to come up with laboratory medicine best practices, and it might be a good way of giving some guidance as to what works best.

DR. HARPER: We'd be really interested in hearing about that from CDC or any group actually. Actually, later this afternoon this may be a good question for Dawn Hanson. He's going to be talking about risk mitigation in hospitals. So she may have -- I don't want to put Dawn on the spot, so it's okay if we don't hear from this, but I don't personally have information on how effective training programs are, but I would be really interested in hearing that as well.

UNIDENTIFIED SPEAKER: As a curmudgeon, I'd like to take on my wine inebriated laboratorians and actually select -- and I'm not sure it's reasonable to say that manufacturers should select the most accurate lots to go to the hospital and therefore lower the overall accuracy for patients not going to the hospital.

DR. BENSON: I don't think in any way we would want that, either.

UNIDENTIFIED SPEAKER: No, but that's what he was suggesting. He was suggesting that they could stretch themselves, take their best lots which meant 12.5 percent, put those in the hospital, and leave the rest for the patients not going to the hospital.

DR. HARPER: Well, they were discussing hospital, but he didn't exclude lay users.

DR. BENSON: Right.

DR. HARPER: But I would like to point out that this is definitely an issue that we've heard about, that manufacturing criteria may vary quite broadly between manufacturers, and sometimes it may be that the criteria used sometimes is the ISO criteria

itself. So it would be interesting to see what people think would be reasonable acceptance criteria for manufacturing lot release. Because that really has a bit impact on performance in the field.

DR. KIECHLE: Fritz Kiechle from Florida. I was a part of that conversation, and we did not emphasize hospital use only. It was strictly a guideline for everywhere.

I wanted to address the issue of training. There have been some studies published, I believe from the Cleveland Clinic, that illustrate very clearly that if one chooses to place the trainee in front of a videotape or CD or some other computerized learning tool, that they will fail a recertification test much more frequently than someone that actually has like 4 on 1 personalized training activity that lasts for at least an hour. So you actually have to sort of see it then do it and then teach it. The old rule still works, and it works very well. It's then embroiled in the brain and stays there.

And we have continued to hire people as point of care coordinators to carry out this kind of

retraining recertification program so we have enough of them to actually do it one on one.

DR. WHITE: I'm Neil White from Washington University in St. Louis. I just want to maybe be a curmudgeon as well. I think we have to consider that there may be two -- that we need to have two different sets of standards. 12.5 percent may not be adequate for safety in an ICU-type glycemic control setting. That's not to say that we can't do better for the patients in the field, but if getting to the standard that needs to be used in an ICU setting produces a product which for one reason or another, cost or size or usability is not appropriate in the field, then we may have to have two different sets of products and two different sets of standards.

DR. HIRSCH: Okay, what we're going to do is we're going to move on, since it doesn't appear we can get this slide deck open. Our next speaker, Dr. Jim Rollins from the Center of Medicare and Medicaid Services in Baltimore, has agreed to give his presentation without slides, which I think is quite noble and brave. Dr. Rollins is going to talk about

the payer perspective reimbursement issues associated with glycemic control. And this talk is not being sponsored by Microsoft, I take it. Dr. Rollins?

DR. ROLLINS: Thank you. Actually, I'm a Mac man, but that's okay. Good morning. My name is Jim Rollins, and I'm the Director of the Division of Items and Services for Medicare. And I'm here today to discuss Medicare's position on home glucose monitoring.

Actually, I had a quote but you can't see.

But I'll read part of the quote for you. This was a quote that was taken from a famous case in Virginia, which describes the complexities of what we have to deal with when considering coverage of items and services. And the quote goes this way:

"There can be no doubt but that the statutes and provisions in question involving the financing of Medicare and Medicaid are among the most completely impenetrable text within human experience." And I'll stop at that. As I said, I don't have slides, but all of this will be on slides, which we can make available later.

The Social Security Act, 1862 (a)(1)(A), gives Medicare the authority to cover or noncover items or services. But in order for items or services to be covered, they must meet three criteria. Number one, they must fall within at least one of the benefit categories established by the Social Security Act; number two, the item or service must not be specifically excluded by the Act; and number three, the item or service must be reasonable and necessary.

Let's look at some of the requirements for coverage. First, the need for an item or service to fall within at least one or the benefit categories.

The Social Security Act lists a number of benefit categories. A few examples are: hospital services, physician services or incident to, as well as drugs and biologicals that are not self-administered. When looking at home glucose monitors, they fall within the Durable Medical Equipment benefit category, also known as DME. DME characteristics include, they can withstand repeated uses; they're primarily and customarily used to serve a medical purpose; they generally are not useful to a person in

the absence or illness; and they are appropriate in the patient's home.

Reasonable and necessary is another rquir3ment as stated in the Social Security Act. It states, quote, "No payment may be made for items or services which except for items and services described in a succeeding subparagraph, are not reasonable or necessary for the diagnosis or treatment of illness or injury, or to improve the functioning of a malformed body member." When determining if an item or service is reasonable or necessary, Medicare must make sure that patients within the Medicare population receive a clinically meaningful benefit from that item or service. Reasonable and necessary requires Medicare to consider the following questions when evaluating an item or service. Number one, does it improve health outcomes from the Medicare population? Number two, is it generalizable to the Medicare population? And number three, is it generalizable to the general provider community?

And let me make a quick aside. Medicare, currently we have about 44 million beneficiaries.

About 85 percent of those beneficiaries are 65 and older. Fourteen percent get Medicare because they're on disability, and then one percent for persons who have in stage renal disease. So when we refer to Medicare beneficiary and when we look at evidence which supports the use in this particular population, we basically look for evidence which supports based on persons being 65 and older.

The next slide I was going to show you was going to be a graphic presentation of the NCD process. NCD is short for National Coverage of Determination. And these are the measures that we put in place in determining whether or not we're going to cover an item or a service. National Coverage of Determination, also known as NCDs, can be internally or externally generated. We follow a timeline. Normally the timeline is about nine months, but sometimes it can be modified if there's going to be a technology assessment or a MEDCAC review on the topic. The Social Security Act states that there must be a benefit category, and in performing an NCD we also have to confirm that that particular item or service

does fall under a particular benefit category. The NCD process is evidence based. It's used to identify peer-reviewed medical literature to determine the effectiveness of an item or a service that is requested. And after public comment, a final decision memorandum is produced, stating either coverage or noncoverage for that particular item or service.

The Code of Federal Regulation also addresses items or services covered by Medicare. This document specifically addresses the different diagnostic tests performed on beneficiaries, the provider who is treating the beneficiary for the medical problem, and how the results of the test are handled by the provider.

Now, we're going to look specifically at the use of glucose monitoring in the Medicare population. In 2009, Medicare spent almost $2 billon on glucose testing and supply. Almost 17 million claims were generated. By comparison, during that same time period, Medicare spent about $2 billion on oxygen and equipment, and almost $1 billion on power mobility devices.

Now, we're going to take a look at the history of coverage for glucose monitoring by Medicare. There are two separate benefits for Medicare that Medicare can use to cover home glucose monitoring. One I mentioned earlier was the DME benefit, and the second one ice the diabetic supply benefit. Prior to the Balanced Budget Act of 1997, Medicare covered home glucose monitoring only for insulin dependent diabetics. But after this Act was initiated, it started supplying this benefit to non-insulin dependent diabetics.

Earlier I talked about the NCD process. There's a similar process that's known as LCD, which is short for local coverage determination. And it basically follows the same type of process in terms of evaluating the medical literature to determine whether or not a particular item or service is found to be effective. CMS has both NCDs as well as LCDs, which adjust the use of home glucose monitoring. In general, the NCDs define the device that can be used as well as the patient criteria; whereas, the LCDs define accessories, supplies, as well as utilization

of the device. When reviewing the NCD, it specifically states patients' criteria, which are the following. Number one, the patient must have a diagnosis of diabetes. Number two, it includes the requirement that the treating physician must state that the patient or an authorized caregiver is capable of being trained to use the device and monitor the patient. And number three, the document designates that the device is designed for home use rather than for clinical use.

Also, because of visual impairment as a potential complication of diabetes, Medicare also has authorized the use of special devices for persons suffering with this affliction. These devices are reliable, accurate, and some devices also include voice synthesizers as well as automatic timers. In order for a patient to qualify for these special devices, the treating physician must certify that the beneficiary is visually impaired and its severity is so that it requires the use of these special devices.

Now, let's take a look at the LCDs. As I noted before, they generally define accessories as

well as supplies as well as utilization use. LCD qualification of supplies and accessories include the following: that the patient must have a diagnosis of diabetes; that the glucose monitor, accessories and supplies must be ordered by the treating physician and they must maintain records on that treatment; and also, that there must be patient or caregiver training on the device.

Other LCD requirements include the maintenance of records of the glucose results and the fact that the device is designed for home use only. The LCD also gives guidance on utilization use. These guidelines note that non-insulin dependent diabetics can get up to

100 test strips and lancets every three months, while insulin-dependent diabetics can get up to 400 test strips and lancets every three months. These guidelines also state that higher amounts are available and are covered if justified by clinical documentation which must be submitted by the provider. LCDs also note requirement criteria for supplies as well as accessories, and these include: that coverage

criteria for glucose monitors must be met; that the treating physician has seen the patient and addressed diabetes care one year prior to dispensing the supplies; that during the time of the visit there is documentation of the type of therapy, and for those who are treated with insulin, the number of daily injections; and number four, that the beneficiary has nearly exhausted the supply of items dispensed.

So in summary, let me conclude by saying, number one, CMS does have the statutory authority to cover home glucose monitoring devices, supplies and accessories. Number two, CMS uses both the NCD process as well as the LCD process to govern the use of glucose monitoring. And number three, patients who have insulin-dependent diabetes as well as non-insulin dependent diabetes are eligible for glucose monitors supplies as well as accessories. And that's it.

DR. HIRSCH: Yeah, we'll be able to make the slides available. Yes, we'll be able to put them up on the Web site.

DR. PINKOS: No, they should e-mail me. My name's Arleene Pinkos, and my name appears in the

Federal Register announcement. They won't go up on the Web site.

DR. HIRSCH: Questions for Dr. Rollins? I'm going to start. I am the medical director of a large academic diabetes clinic at the University of Washington in Seattle. And one of the things that is exploding right now, and I'm not sure people appreciate the fact that the number of people with Type 1 diabetes in Medicare age over the age of 65 is exploding. I don't know what the actual numbers are, but as this population is living longer and doing better, they are reaching Medicare age.

And I think that there are a lot of issues with this that we are not prepared to deal with, because up until now Type 1 diabetes has mostly been a pediatric disease. Well, it's now become a geriatric disease. And so, the question I have for you as you were going through what Medicare covers in terms of home blood glucose monitoring supplies -- as we have these patients both on pumps and frequent, frequent testing, we showed in a March ADRF trial as an example that these patients are checking six, seven, eight

times were day, and that's an average. And I guess the issue is is that for these patients with Type 1 diabetes, three strips a day is never enough for this population. And what it does is it just adds to the more of the burden of documentation. And I'm wondering if there are any plans for this older population with Type 1 diabetes, if we can do something to sort of ease this documentation burden that we are all facing as these patients are successfully entering the age of geriatrics?

DR. ROLLINS: I think that CMS would be willing to consider modifying documentation. I think that if you've got a patient who's using four, five, six seven strips a day, does that mean that that patient needs to have all of that documented on that log? I think that there are things that can be put in place that can address that. So I would say that I think that CMS can yes, can accommodate this.

DR. HIRSCH: Okay. And I will just say what we do, which I've never seen CMS or anybody really talk about, is using electronic medical records and electronic downloadings of the meters making this very

simple. It does simplify it, and I just put a plead out to clinicians and CMS and also the industry about pushing the technology -- actually very old technology that can make this documentation much easier than I think most people have to struggle with now.

DR. ROLLINS: I think electronic downloads is an excellent example of a new technology which CMS as well as I'm pretty sure a lot of other commercial insurers are willing to embrace. As long as there's documentation -- and as I say I can't speak for other companies and I can't say that currently we have things set up that way. But I do think as I say, electronic documentation an downloading of those results to show that those activities did take place, is something that we would encourage.

DR. HIRSCH: Great. Claudia?

DR. GRAHAM: Yes, Claudia Graham with DexCom from San Diego, California. Could you comment on the in-patient tight glycemic control with regards to Medicare payment, DRGs, compensation back to the hospital. I think there's some confusion perhaps existing, and where Medicare may be going with regard

to in-patient payment?

DR. ROLLINS: I really cannot address that. All I can say basically is I would make the assumption that reimbursement would be a part of the DRG. That's all I can say.

DR. HIRSCH: David?

DR. KLONOFF: David Klonoff, Mills Peninsula Health Services, San Mateo. You mentioned that training is needed to receive coverage. What type of training for blood glucose monitoring are you referring to? Is it class or learning from the doc ? would this be enrolling in a class or working with a doctor or an educator?

DR. ROLLINS: I think working with a doctor, or working with an educator. And I think that a lot of physician offices may be associated with a diabetic educator or something on that order. That would be sufficient in terms of documenting that the patient or the caregiver has been trained on using that particular device.

DR. KLONOFF: Are you requiring that documentation currently?

DR. ROLLINS: We do require documetnatio that the patient or the caregiver has been shown ? and are proficient in using the device.

DR. KLONOFF: Thank you.

DR. CASABURI: Good morning. Two questions to the Panel. I'm Dan Casaaburi from Sanofi-aventis. And the first question I have is, does Medicare have a policy on reimbursement for continuous glucose monitoring systems at this time? And then secondly, a question to the Panel with regard to the use of continuous glucose monitoring systems, not necessarily to drive insulin dosage, but perhaps has an alarm system for hypoglycemia. And that is somewhat of an off-label use in the Type 1 pediatric population at this time.

DR. ROLLINS: Actually, I can answer the -- let me try the first one first. Actually, somebody in the audience I think might be able to answer both of those questions. It just so happens that one of my colleagues is here. And she was the one who was actually responsible for one of the MEDCACs that we had specifically addressing the use of glucose

monitoring devices., Dr. Beth Koller. I think she can answer both of those questions.

DR. CASABURI: Okay, first question is that the Medicare's position with regard to reimbursement on continuous glucose monitoring systems. And then the second one is more of a general regulatory question or medical question.

DR. KOLLER: I'll do one at a time.

DR. CASABURI: Well, about -- go ahead.

DR. KOLLER: Okay. As Dr. Rollins indicated, Medicare makes its decisions and implements its decisions at two levels. The first is at a national level. And that's a decision that is made. Once that decision is made it applies uniformly across the country. Whereas -- most people are not really familiar with this, but many decisions for Medicare are made at the level of the local contractors. And this is just a reflection of the historical development of the Medicare program in which centralization -- there were concerns about centralization of medical care delivery and decision-making.

And at this time, decisions on continuous glucose monitors are made at the level of the local contractors. But the local contractors have significant amount of experience in terms of understanding glucose monitoring and our patient population. We also have another decision in place which has some bearing on this. We do cover and have a national decision for insulin pumps. And insulin pumps can be provided to only a limited number of patients who fit certain criteria. They have to demonstrate additional need in terms of problems in terms of maintaining glycemic control -- having problems with excess, hypoglycemia, et cetera.

And so in general, the contract medical directors, the local contractors, have provided continuous glucose monitoring only to that subset who are on pumps. They may choose to also provide continuous glucose monitoring for a shorter interval -- for example, a short stay, 72 hours, et cetera, so that someone can obtain information so that they can guide their therapies, that they can investigate nocturnal hypoglycemia, et cetera. But that decision

is not at a national level; it's a level of the local contractor. So you have to justify it. One of the other things --

DR. HIRSCH: Dr. Koller, we are about out of time. If you want to do the second question very quickly.

DR. HARPER: I can answer the second question.

DR. CASABURI: Okay, go ahead. Thank you.

DR. HARPER: So currently, continuous glucose monitors are only actually approved for tracking and trending. So they aren't approved for any sort of a replacement of the functions of glucose meters. However, the encouraging part is, it's part of the development of an artificial pancreas. There are investigators who are actually looking into doing studies, and then there are some that are well on the way of performing studies to evaluate the performance of CGMs to see whether or not they could be effective in alerting patients who might be hypoglycemic -- especially at night, they're starting at night. So we are encouraged by that.

DR. HIRSCH: Dr. Pinkos? Arleen?

DR. CASABURI: I just wanted to invite Dr. Hirsch to comment on that, with his extensive experience in Type 1s and pediatrics, the use of glucose monitor -- continuous glucose monitoring.

DR. HIRSCH: My bottom line is, we are not quite there yet. We're getting closer. I'm very excited about the future, but right now as we sit here in 2010 we're not quite ready yet to do that.

DR. PINKOS: Just a quick question. Pinkos, FDA. As much of technology is driven by reimbursement, is there any potential for higher reimbursement for more accurate point of care meters, and if so, what would have to be done to support that?

DR. ROLLINS: Actually, the area that I'm responsible for, coverage analysis group, we have nothing to do with reimbursement. That actually falls under a different part of CMS called CMM. So in terms of reimbursement, I really could not address that.

DR. HIRSCH: Okay. Thank you all very much. It is now time for our break at the Grand Foyer. We will meet back here at exactly 11 o'clock for our next

discussion.

(Pause.)

DR. HIRSCH: Okay, if everybody can have a seat, we're about to get started. And while you're finding your seat, I'm going to make an announcement here, that we would encourage those of you who are actually in the trenches seeing patients in the hospital, specifically in the ICUs, to feel free to come up and comment on some of these issues that we are discussing this morning.

Our next talk is going to be by Dr. Rich Bergenstal, who is the Executive Director at the International Diabetes Center outside of Minneapolis. Rich is a good friend of mine for many years, who also right now is President of Science and Medicine for the American Diabetes Association. And Rich is going to talk to us about Advantages of Tight Glycemic Control in the Hospital Setting.

DR. BERGENSTAL: Thank you very much, Irl and thank you, Courtney and Arleene and others for the invitation to have an opportunity to join in this dialogue today. I will give you my conflicts. My

Center in Minneapolis does lots of clinical trials on almost all new devices and drugs, but no personal compensation is received for any of these. And at the bottom bullet there, I am an officer, volunteer role for the ADA. And as I start off this discussion, which obviously is going to be focused on the hospital, let me start with a few points on the American Diabetes Association and then end with a few points relevant to our discussion I think.

And to yesterday, for those of you who were here, you remember yesterday there was some discussion of how tight is tight enough for the standards? And the American Diabetes Association held a conference back in 1986 that said, when the current total error was around 15 percent, the American Diabetes Association said, well, why shouldn't it be tighter -- always the patient advocate, can we do better -- and said 10 percent. And yet, when they held their next conference in 1993, they realized we really weren't meeting that 10 percent. And yet to the surprise of some, they said, well, let's make it 5 percent.

But let me put the context to that, because

it got brought up a few times yesterday. In June of '93, for those of you who remember, that's when the DCCT results came out and said, dramatic improvements in eye, kidney and nerve disease when you improve the hemoglobin A1C, but there was a significant increase in hypoglycemia. And so in light of that notion that we really need to avoid this hypoglycemia but we really want tight control, that was some of the context around saying, let's try to make the meters as accurate as possible.

If we now put it into to today's perspective in learning what we have, I think that the American Diabetes Association would say that -- and I think the tenor of yesterday's meeting, that glucose monitoring is clearly one important component in safely achieving improved glycemic control -- there didn't seem to be any argument in that yesterday. And that even going to the point of non-insulin users, the IDF recently ? many of you in the room were part of a panel that said, if you actually record the purpose of the testing for non- insulin users and instruct them on how to use the data, it can be helpful. And you may

have seen last, couple weeks ago even the National Health Service in England - - not always the most generous in their supplies ? has said that even the non-insulin users, if there is a plan for how to use the data and some documentations of this plan, that it makes some sense. So I think following on the theme of the last discussion of having in the record that you are actually using the data, it can be helpful.

So we're really not achieving our goals overall very well yet. And yesterday it came up again, well, hypoglycemia seems to be a major factor. How much of this is meter-related versus other factors? And I will just share with you a little bit of data from the Accord trial that said, what we documented was that the biggest factor was actually not carb counting actually or changing meals. Nowhere on the Top Ten list was meter inaccuracy, but then I don't think it was really looked for carefully. Did we ask our patients, did we test their meters? So clearly it may be a factor, but we have many other factors that clearly need to be overcome to improve control. So maybe we're using the A1C too much and

not using SMBG in concert enough with it to make our adjustments, and that would be my plea.

So I think that there is room for improved accuracy in the hospital, and that's what we'll talk about. I think the outpatient, there's room for improvement, but it really seems that it has to start in the hospital, but equally should be the efforts on how to use the data. I think that probably deserves equal attention to the improved accuracy. And again, as has been mentioned, continuous glucose monitoring holds great potential with further study and innovation.

So thanks to some of my colleagues -- some are in the room -- and for sharing some data and some slides for me -- here's the problem in the hospital setting, that people with diabetes or abnormal glucoses that you might call pre-diabetes, make up a huge number of patients in the hospital now ? some 12 to 25 percent. In our hospital it's 20 percent at any given time. And in the cardiac surgery patients, it's up to 50 percent of them if you actually test them, have diabetes or impaired glucose tolerant. So we do

need to figure this out and have a good plan of action. It used to be that we didn't worry too much about hyperglycemia and sliding scales, as Dr. Hirsch said was the standard of the day. That is changing, and we are understanding the forces that are leading to high blood sugars and the forces that are leading to low blood sugars. And each of these need their attention if we're go end up in the middle spot of good control without adverse effects.

So thanks to Dr. Furnary, who I believe is still here today, he started tracking some of the deep sternal wound infections and showing they were actually much higher in people with diabetes. And this seemed rather obvious and important. And then when he developed the Portland Protocol of which many of the protocols today are derivatives thereof, started to see these sternal wound infections get less and less. So I think this is one of those facts that's really hard to argue with to say, improved control had a major impact. Then there was the study that we have all heard about and quoted. And whether you call it the Leuven Study or -- the Van den Berghe

Study, really, is how it's usually talked about -- started changing practice. And because a blood sugar 103 versus 153 in that Center with very precise monitoring led to dramatic decreases in mortality, whether you looked at it, mortality getting out of the ICU or survival for the entire hospital stay or transfusions or sepsis or renal insufficiency, several parameters.

So this started to change things and make people start to think about the level of control. Then other data was collected along the way, too, to say that, this seems to be on a population level. The higher the glucoses, the higher the mortality rates. And then back to Dr. Furnary again, the higher the glucoses on average, the higher the mortality rates in post cabbage patients -- even to the point that a blood sugar of 200 in the first post-op sugar could have a seven-fold impact on risk of increasing mortality. So these were the factors that started people thinking that improved glucose control, maybe even very tight glucose control, was critical in the hospital setting.

Then as always happens, there comes a series of data to say, as we look at different patient populations, wait a minute, we're not consistently finding this, that patients in sepsis treated to tight control. And again, the numbers are fairly similar there -- 112 versus 151 -- no difference in mortality. It didn't harm you to get that tight in terms of mortality, but there was more hypoglycemia. And then meta-analysis were starting to be done to say, wait, are we ready for everyone to be at a blood sugar of 100? There really was no change in overall mortality when you put all the studies together, but there was some increase in hypoglycemia. So how tight is tight enough? American Diabetes Association and Association of Clinical Endocrinologists got together and said, well, let's work on this. And they were working on this and putting all of these data that I just showed you and several others in context. And as they were deliberating, another study came out that we've referred to yesterday several times, but I'll just briefly mention again -- the NICE-SUGAR study.

So this working group was meeting, and then

these results were released. And so it obviously had a significant influence on their deliberations because this was the largest trial ? 6,000 patients ? who were now randomized to tight control, or I won't say usual control, I'll say good control -- so good control versus very good control in 40 centers using somewhat standard approach. Although, as we heard yesterday, standard meaning targets but not necessarily how the glucose was measured in all sites and was hard to determine arterial venous capillary. But they did get a separation of glucose control over time, and yet that separation, the lower, tighter control over time actually led to a slightly increased mortality, a 14 percent increase, or a 2.6 percent absolute increase. And there was more hypoglycemia, as we at the bottom line there, had talked about yesterday -- some 13 to 14-fold increase. And there's the 90-day mortality data highlighted in the middle.

So with this, the discussion said, well, the standard group of 140 to 180 had reasonable outcomes ? still what we would consider good control. The group going from 80 to 110 had no significant benefit over

that group. So that maybe the new standard should be closer to what we would say, good control in this 140 to 180 range, although not tested was obviously that in-between group of, how about 110 to 140. And when you look at another nice paper in circulation in 2008 that sort of plots the in-hospital mortality after acute MIs, you can see that the lowest point seems to be somewhere down around that 110 mark and goes up on both sides of that, so that if it were possible to get there safely and not overshoot, that somewhere around that 110 to 140 would be a reasonable goal if we can find a way to get there safely, whether that's better protocols, more accurate measurement, better training - - all of the factors that go into actually achieving this safely.

So the conclusions of the working group making a joint statement was that good control is important; that near normal control, we're not there quite yet; that by no means should we go back to the laissez-faire days of over 180; that 140 to 180 makes sense but probably 110 to 140 in hospitals and settings that can do it safely and have shown that is

reasonable, but again deserves to be tested; and finally, avoiding hypoglycemia is critical. I think I'll skip the outpatient, because I have a feeling Dr. Hirsch will be talking about it. But I'll just mention that IV protocols are critically important that they're used effectively and people are trained. You can get good results when they are implemented in a systematic way. There's lots of criteria to say what makes a really good protocol and it really has to do mostly with training of the staff to implement them carefully.

In the non-ICU setting, I think it's equally important to understand the physiology of insulin and to have orders that utilize the principles ? I'm going to go straight to this of ? I like my friend, Dr. Inzuci's BBC for those of you who listen to the radio ? the basal, bolus and correction. IN our hospital we call it a complete insulin order. We try to enforce, do not take off an insulin order that does not have three parts to it written: a background insulin, a mealtime, standard dose and a small correction factor. That I think is how to do it safely

in the non-ICU setting. Avoiding hypoglycemia, we are learning, seems to be a critical factor. And we come down to whether the meter's at 20 percent and 15 milligrams per deciliter are adequate in the hospital. I would say it's appropriate to be looking at tighter standards in the hospital as the first goal to minimize this risk of hypoglycemia and allow people the confidence to continue to improve control.

And finally, let's look at whether there's anything new coming. I'll show you one bit of data, because it came up yesterday several times. There's one continuous glucose monitoring system that was presented last week in Europe, not approved in the U.S. But just to show you that continually monitoring intravenous blood sugars can get MARDs or MAREs around six percent, and almost all of the values in the A-B zone. And this was the first 19 patients actually done in the hospital setting. And you can see pretty reasonable values, but I think what's even more important is this continuous printout. Imagine this now, if this were implemented, that you actually could see, have confidence in the values and be able to

detect a low one, that you can't do even doing every two-hour blood sugars or every four-hour YSIs as was done here.

So this technology, if continued to be proven safe and accurate, I think holds a great promise to say, can we get closer to that 100 to 140 or near normal and avoid hypoglycemia. Then we may be able to really prove the true value of near normal blood sugars, which we're having difficulty at the moment safely achieving.

So final bit of advice in conclusion for this Panel is that I think the FDA ISO, the CLIA-POC, which we talked about all three of these yesterday quite a bit, are doing really important work to gather this data and to write standards and guidelines. But people with diabetes and practitioners don't always look to ISO or CLIA for their main information. They're looking to other organizations like the ADA Diabetes Forecast or the standards of care that come out every year. So that this partnering with these agencies and professional organizations I think is going to be the key if we're really going to change

practice and get people using the devices the way they're supposed to be used to improve control and get us to the point where we need to be. So thank you, and maybe we have time for a question.

DR. HIRSCH: Dr. Hellman, you go first.

DR. HELLMAN: Richard, again, thank you for your comments. As one of the people who was part of the Panel, along with Irl and many other people, one of our great concerns we had was the issue of the accuracy of the glucose meters. Because there are critical situations in the hospitals.

But one of the things that resulted I think in part from that, was there was a letter to the FDA written by one of the past presidents of ACE and signed by the President and another, asking specifically for a 10 percent accuracy threshold. And one of the things that is a concern and I wanted to ask you, is has the American Diabetes Association specifically considered a similar type of request? Because one of the things that I have a problem with -- there's no question that the hospital needs this accuracy -- but I don't know how to define the people

who are at great risk. Should we be telling people, these meters that you have are good, but please don't drive a commercial vehicle or go up a high ladder because they're not really as accurate as they should be for you in that setting when it's critical to know that? It seems more reasonable to have an across-the-board recommendation as a first effort, even if technically you have different devices for the hospitals. Has the ADA considered the position like that? Because I would encourage it.

DR. BERGENSTAL: Well, I think the ADA is thinking about this and is very interested in the output of this meeting to maybe it's time to convene another panel. Having been from 86 to 93, it's probably time to have this discussion again. Because I think it's ADA and ACE and others getting together who are going to do the translation of this sort of work into practice. So it may be time to seriously consider that.

DR. HELLMAN: Thank you for letting me put you on the spot.

DR. HIRSCH: Dr. Furnary? Richard?

DR. FURNARY: That was a very nice talk. Thanks very much. And I think it's important. The topic of your talk is advantages of tight glycemic control. I think it's important that the FDA hear -- and that's Courtney and Carol and everyone else -- hear what these real human advantages are, because yesterday, Courtney presented and Carol presented today, the disadvantages of hypoglycemia. And we heard that there were 100 deaths that occurred between 1992 and 2009. And that's terrible. I hate that. But even worse are the deaths that have occurred from hyperglycemia in the same period. Now, if we just look at the cardiac surgery database -- I'm probably the only cardiac surgeon in the room silly enough to be here -- between 2000 and 2009, the Society of Thoracic Surgeons database. For patients with diabetes, the mortality rate in this country was 3.6 percent. That's about 6 million patients.

At the same time, in Portland, our mortality in the same years was 0.9 percent -- one-quarter of the national mortality. Now, it's either I'm the best surgeon in the world and my partners, which I don't

believe, or the fact that we keep our patients at 7110 made a difference. And if you calculate he number of deaths in those 6 million patients over 10 years. If you take down the 2.7 percent, there are over 150,000 people in 10 years who would have suffered because of hyperglycemia -- 2.7 percent of 6 million. That's a huge number, and it's much bigger than 100 patients.

We can't lose sight of that. In Portland, one out of 11 patients with diabetes dies after open-heart surgery. In the rest of the country, it's about one out of 28. That's a huge difference. And we did this entire thing, Courtney and Carol and everybody and Arleene at the FDA, with current hand-held meters, with a 20 percent error. We didn't kill anyone from hypoglycemia. I think it's fantastic that we should get better and more accurate meters, but it's not just the meter. You can't put the entire weight of TGC on a meter, because the protocol matters. One of the biggest differences as Dieter will probably talk about, is it's the protocol that matters, and how frequently you measure and how long they're hypoglycemic.

In our patient population, less than 5 percent of patients at 7110 go below 60, and the average time below 60 before they get above 70 is 33 minutes. That's why there's no consequences of hypoglycemia. Yes, it's better to have a good meter, but it's even better to have a good protocol. I know you can't regulate a protocol, but you can't put the weight of the entire TGC onto the meter. And I think it's a very important thing for everyone to hear.

DR. HIRSCH: Thank you, Tony. Very much appreciate your comments, but we need to move on. Rich, thank you very much. Our next speaker is going to talk about why tight glycemia control may not be appropriate in hospital settings, by Dieter Mesotten, who's an anesthetist and intensivist at the University Hospitals in Lueven. And when we met this morning, I said, so you are a colleague of Dr. Van den Berghe? He says, no, I'm a disciple. And so that's the difference. We look very much forward to your comments.

DR. MESOTTEN: Thanks a lot for the nice introduction. First, I would like to thank the FDA

for giving me the opportunity to talk about why tight glycemic control may not be appropriate in hospital settings. And that's a big like asking Bill Gates to promote upcoming iPod from Microsoft.

So my talk will revolve around two main issues: first of all, about the clinical validity of tight glycemic control, and secondly about methodology to do tight glycemic control. And we all know from association studies that there's a J shape relationship between risk of mortality and blood glucose levels. So the lowest risk of dying you have when you're on admission blood glucose levels, or your mean levels across your ISU state are within the normal range. And for adults this means 82, about 120, 130. So as soon as blood glucose levels go up, you have an increased risk of dying in the ICU. And the same accounts for the hypoglycemic range.

So association studies cannot delineate whether hyperglycemia is adaptive. Maybe it's a good thing and it's part of the survival response, or maybe it has nothing to do with the risk of mortality; it's just an innocent bystander. It may also be an

actively contributing factor to adverse outcome. And to test this hypothesis, back in '99, we started our first study. And that hypothesis was to test whether hypoglycemia was not an adaptive response.

In the first study we tested the do not touch strategy, so the comparator, which will be represented by the red lines throughout my talk, versus a strict normal glycemic intervention group. And this study was done in a surgical ICU. In this study, 1,548 patients were randomized over 12 months' period of time. Once again, tight glycemic control in French group, maintained blood glucose levels, keeping between 80 and 110 milligrams per deciliter. The conventional group here on the insulization was started, as soon as blood glucose level exceeded the limit of 215 milligrams per deciliter, during that threshold, above which you would get fluid shifts and hypertension. It's very important that the insulization was stopped as soon as blood glucose levels went below 180 milligrams per deciliter.

And we all know from this study that tight glycemic control reduced ICU mortality from 8 to 4.6

percent. But there was a price for it. Hyperglycemia, defined as blood glucose levels less than 40 milligrams per deciliter, went up from 0.8 to 5.1 percent. And if you put this graphically, you can clearly see that this survival benefit was maintained throughout the entire hospital setting, from the ICU as well as in the hospital. And even more, the benefits of tight glycemic control were much more pronounced in the patients that would stay in the ICU for more than three days -- the so-called long-stay ICU patients. And here, you had an absolute risk reduction of about 8 percent.

As a first step to test generalizability -- and we've been talking about it several times -- we took the same protocol, the same experiment, to our medical ICU, which is right across the corridor in a hospital. And this study was powered to detect a 4 percent absolute risk reduction in the long-stay ICU patients -- so patients with an expected stay in the ICU for more than three days. In this study, a total of 1,200 patients were randomized, leaving us with 767 long-stay ICU patients over three-year periods of

time. Once again, I would like to emphasize it had the same design. In this study, we saw that intention to treat population, so the 1,200 patients that tight glycemic control, non-significantly reduced ICU mortality from about 27 to 24 percent -- absolute risk reduction of about 3 percent. However, for the long-stay patient population, so the target group in this study, it's decreased ICU mortality from 38 to 31 percent -- and here, with even a bigger increase in hypoglycemia. It went from 3 to about 19 percent, which is really high.

I said before, the medical ICU study was not powered to detect a mortality difference in intention to treat population. Therefore, we combined two study populations in the mixed ICU population. So we had 2,748 patients. And on the left-hand panel you can clearly appreciate that tight glycemic controlled decreased the mortality risk from 24 to 20 percent. And looking at long-stay ICU patients, it went from 38 to 30 percent. So we're talking about for the overall population, 4 percent absolute risk reduction, and for the prolonged ICU patient population, a decrease of 8

percent.

As a final step, we took it to our pediatric ICU population. And here, we had even a more tighter blood glucose control. In infants, which meant pediatric patients less than one years of age, we were targeting 50 to 80 milligrams per deciliter. Children defined as the age between 1 and 16 years old, was our target range, 70 to 100 milligrams per deciliter. Once again, our comparative was a strictly do not touch strategy. Here in translation was also only started when blood glucose levels exceed 215 milligrams per deciliter. And different to the other studies, the primary ambient was length of stay. And a study was powered to detect the difference in inflammation measured by C-reactive protein, as baseline risk of dying in the pediatric ICU is only 5 percent and it's really hard to show a much harder difference.

In total we recruited seven patients, mostly after cardiac surgery. And to a great surprise, even in this population, we saw significantly mortality reduction in our pediatric population. It went down

from 5.7 percent to 2.6 percent; once again, an absolute risk reduction of 3.1 percent, consistent over the three trials. And here, hypoglycemia defined as blood glucose levels less than 14 milligrams per deciliter, went up from 1 to 25 percent. However, needless to say, it was not unexpected, because we were targeting in our neonates levels of 50 to 80 milligrams per deciliter, which is really close to the threshold for hypoglycemia.

So I think it's fair to conclude that from our Leuven studies that compared to the do not touch strategy, achieving tight glycemic control improves the outcome of ICU patients, measured by maturity but also measured by morbidity; for example, intervention and perfection, less transfusions, less need for prolonged ventilation and a decrease in critical illness polyneuropathy. And these findings were further corroborated by our mechanistical studies. Tight glycemic control improved mitochondrial function, it improved the kidney, cardiac function. It also reduced a material activation and it improved leukocyte function and reduce inflammation.

But I do have to warn you, there is a specific setting in which these studies were done. First of all, we're talking about three independent single center trials, with a high study inclusion rate; 95 percent in surgical ICU, 60 in the medical and 68 in the pediatric ICU. We had a very passionate PI, Professor (inaudible), and a nursing staff that were fully dedicated to tight glycemic control. I also have to mention that most blood glucose measurements were done thorough arterial sampling. Blood glucose analyzer was the only device in the surgical and pediatric study, and the medical ICU, the only device that was used was the HEMAQ. Insulin infusion was only done through a central line and using a very accurate syringe pump system. So this is talking about a center with experience, passion and adequate technology. And you can summarize in one word, standardization in a proven concept design.

We all know about the enthusiasm and the raving about these studies and implementation in different protocols across the world. And many people try to do follow-up studies to confirm our data in

Leuven, whether from multi centers, single center studies, five-step glucose control, Arabi, De La Rosa and many others. However, the results are rather disappointing. And I think there was some major flaws. First of all, the multi center trials had to be stopped due to increase in hypoglycemia, which was not unexpected if you had read the Leuven studies. There was also an inadequate separation of the glycemic levels in both treatment groups. They could not reach their targets. And these two factors caused that all studies were under-powered to detect mortality differences. So we cannot draw conclusions from these studies.

And to address those statistical trial design trial issues, the NICE-SUGAR trial was set up. And once again -- we've talked about this many times -- so this study randomized 6,104 patients that were expected to require an ICU state of more than three days, a bit like our medical ICU study. This study was powered to detect a 3.8 absolute risk reduction in a 90-day mortality, assuming a baseline risk mortality of 30 percent. In the tight interventional group,

they were looking at levels of 80 to 110. However, the big difference is in the comparator. The conventional group, here they were aiming for levels between 180, and insulin infusions were stopped as soon as they went below 144. And to everyone's great surprise, even for the investigators in the NICE-SUGAR trial, they saw an increase in mortality with tighter glycemic control, absolute risk increase of 2.6 percent. So this study was really the mirror image of the Leuven trials.

And now everyone is really puzzled and do wonder, how could we possibly explain these different outcomes? I would like to emphasize two things:

first, design and secondly, the intervention itself. It's all clear to you that the Leuven studies were done instead of a single set of trials, while NICE-SUGAR was a very big 42 center multi center trial. We all know that (inaudible) targets were both the same, but there was already a big difference in the control target. In Leuven we were aiming at 182 to 215, in NICE-SUGAR, 144 to 180. And what are the implications for the study itself? If we're looking

at the mean (inaudible) in the Leuven study, comparing control convention group versus the tight glycemic group, you see that there's a mean difference of about 50 milligrams per deciliter. And due to the design in the NICE-SUGAR trial this was reduced to about 25 milligrams per deciliter, indicating a huge overlap in the two study groups, which makes it really hard to show a mortality difference.

So if you put this graphically, you can see that the comparative group in red for the Leuven compared to the one in white for the NICE-SUGAR trial, went down our J-shaped curve. Does it have statistical implications? Yes, it does. Because in fact, NICE- SUGAR was looking at a one percent absolute risk reduction, and such a study would have required 70,000 patients. So there's some statistical problems. But that's not the most important part.

I think further analysis is needed for the intervention at the bedside. What were the nurses doing? What were the doctors doing? And here, there's a big difference. In Leuven we were working with a very generic guideline. We want to stimulate

intuitive decision making by the nurses. NICE-SUGAR, we're using a strict if then algorithm with no freedom for the nurses. Insulin in Leuven was only administered as an infusion, using very accurate syringe pumps. In NICE- SUGAR, the protocol allowed infusions as well as both administration of insulin. And all sort of pump were allowed for the metric, syringe pumps, et cetera -- did not even record it. And to build further on this meeting on blood glucose meters, I would like to look further at the sampling and with the course measurements.

In Leuven, we always tried to use arterial blood. And we were measuring in the surgical and pediatric study by a blood gas analyzer. In the NICE-SUGAR trial, everything was allowed -- arterial, capillary, venous, and they used diverse matters to measure it. They did not even record it. They say, with use of point of care glucose meters, our blood gas analyzers are laboratory analyzed in routine use at each hospital.

Does this affect results? And I think so. And these are adopted from Duncan Young presented at

the Brussels Intensive Care meeting last year. And here we're looking at that, our duplicate measurements from ICU patients. And we were looking at the 95 percent confidence level. The 95 confidence is grossly the area between our limits of agreement, so the 1.95 standard deviation on both sides, so the mean. And we see that the most accurate one is a blood gas analyzer, so got a 95 percent confidence level of about 14 milligrams per deciliter. If you compare to the gold standard, the laboratory, it goes up to 21.6 milligrams per deciliter. If you look at example at the HemoCue, which was used in a medical study as well as in the Visup (ph) trial, it's about the same, 20 milligrams per deciliter. But the worst thing is that you're using capillary blood on strip point of care blood glucose meters. Here, you've got a 95 percent confidence interval of 37.8 milligrams per deciliter. And even worse is mixing matters, which happened in a NICE-SUGAR trial. One time you use a blood gas analyzer, the other time the laboratory, and the other time you use a point of care blood glucose meter to steer your insulin infusion to get to tight

glycemic control. Here, the 95 percent confidence interval is 50.4 milligrams per deciliter. And this should be seen in the background of your entire glycemic control target range, which is only 30 milligrams per deciliter. So strip point of care and mixed matters, they exceed this in limits.

So if you take a little closer look and compare it with the center lab techniques, you see that if you take the current ISO standards, allowing 20 percent error, a blood gas analyzer you've only 1 percent out of this 20 percent error range. If you take arterial blood with a blood gas meter, you see already 12 percent gets out of the range. And even worse, and I think it's really unacceptable, when you use capillary blood in a point of care blood glucose meter, it goes up to 27 percent outside the target range.

We did the study ourselves in the background of an expert setting in tight glycemic control management. And we compared two point of care meters against the APL blood gas analyzer in 37 patients. And you see for both point of care blood glucose

meters, they all exceeded in the 95 percent confidence interval, the target range for tight glycemic control. For the AccuChek it was 40.5 milligrams per deciliter; for the HemoCue, it was 37.1 milligrams per deciliter. So your confidence interval for accuracy of your measurement is bigger than your target range.

And our data were confirmed by a study in the Netherlands, comparing blood glucose meters against another blood gas analyzer, the rapid lab blood gas analyzer by Siemens, using different technology. And also there, you saw that the 95 confidence intervals greatly exceeded the target range in tight glycemic control. For the AccuChek, this Dutch study, it was 61.2 milligrams per deciliter, and for the HemaCue it was 39.2 milligrams per deciliter.

How is this possible that these point of care blood glucose meters are performing well in the outpatient world and for ambulatory diabetics and not in the ICU? And we've been talking about it a lot yesterday, the interfering factors, such as catecholamine therapy, adrenalin, no adrenaline, anemia, which is prevalent in the ICU population --

also drugs. Ascorbic acid is given intravenously in the ICU patients, the confusion between capillary, arterial blood. And I'm pretty sure there are many, many unknown factors that interfere with this point of care diagnostics.

I also would like to say that blood glucose measurements do not stand on their own. And all clinicians, among us they know. When you do give high dose of insulin, you lower potassium levels. In Leuven there's a standing order. You always measure potassium levels when you do a blood glucose check. And it's a standing order to maintain potassium levels above 4 mEq/L. And you do it by supplementing it with IV potassium. And it's clear from a pediatric study that we had 6 percent more potassium levels below 4 mEq/L; however, without an increase in deep hypocholemia. But this with an expense of a 55 percent increase in participant supplements. So you really need to check and do something about your potassium levels when you're doing tight glycemic control.

And I've heard in the audience that speakers

are sometimes not really clear about their statements, so I try to be very clear what I mean and when I interpret this scientific data. For tight glycemic control or any other narrow target range in the ICU, capillary blood sampling is inadequate. And all point of care blood glucose meters are inadequate. And they do not belong in the ICU, and they should be banned. And I think so far, only combined measurements of arterial glucose and potassium in a blood gas analyzer seem appropriate at the moment. What went wrong if you're comparing the Leuven studies to the big multi-center trials? Tight glycemic control and is acknowledged by the scientific as well as the clinical community, is a complex intervention. Proof of concept studies, driven by a scientific question, looking for efficacy in a strictly controlled setting with high internal validity, were immediately extrapolated to confirmation studies. But we're looking at clinical practice, effectiveness, pragmatacism, and external validity of generalizability. However, we underestimated the giant step it was taking. We underestimated our

technology.

And in summary, going back to my title, tight glycemic control may not be appropriate in hospital settings. I'm strongly against the current methodology to do tight glycemic control, but I'm strongly in favor of the scientific concept of tight glycemic control. And with this important J-shaped curve, I would like to say that I'm available for all your questions. Thank you for your attention.

DR. IRL HIRSCH: Thank you for that wonderful presentation. We're going to do this quickly. Are there any burning questions, because we are a few minutes already over time. Anybody want to step up to the mike? Of course.

DR. FURNARY: So, just something to think about over our lunch break -- my name's Tony Furnary. I'm from Portland, Oregon. Just some things to think about over the lunch break, and the things that I think we can discuss in the Panel, is that although I agree with your conclusion that tight glycemic control can be done, I disagree that it cannot be done with current devices. Although I agree that arterial is

probably the best way to go, I disagree that it cannot be done with other things, because we've done it for 18 years now, longer than has been done in Leuven. And finally, I think the entire piece of NICE-SUGAR goes away if someone actually reads the paper. And if anyone -- how many people in this room have read the paper? So 90 percent of all the deaths -- remember, there's no difference of mortality in the hospital, no difference of mortality 30 days. The difference in mortality occurred at 90 days. And 90 percent of the deaths in the study group and 91 percent of the deaths in the control group were due to -- who can answer the question besides Irl, because I told him?

(Hands raised.)

DR. FURNARY: DNR withdrawal of care. I don't care how much glucose you give in the first three, five, ten days, it's not going to affect the family's decision to withdraw care 90 days later, end of statement.

DR. HIRSCH: Last question.

DR. CEMBROWSKI: George Cembrowski, University of Alberta. Our hospital participated in a

nice study. While I run the laboratory, I really didn't find out until the tail end. I was able to data mine results that were done both on the same patients within 15 minutes. Whole blood glucose is done on a very popular care system, as well as arterial blood glucose done on the radiometer. And for a while, for at least three strip lots, the manufacturer of this very popular system was biased tied by at least one millimole or 15 or 20 percent, which probably would have resulted in treatment of artifactual hyperglycemia. The manufacturer eventually got the act right, and this will be published soon in Clinical Chemistry. So there are more issues with NICE-SUGAR.

DR. MESOTTEN: I'm looking forward to the data.

(Pause.)

DR. HIRSCH: I'm going to have you find my talk, because I am the last talk before the lunch break. Thank you. I have been asked to talk about current practices and experience of tight glycemic control in the hospital settings. And I think another

name for my talk could be The Reality Check.

What we are really addressing today is current practices of insulin use in the hospital. Please keep in mind, there was little interest in this topic until the publication of the SICU data we just heard about. And there's little teaching about insulin and use for both inpatients and outpatients due to lack of consensus on how to use insulin prior to the era of insulin analogs. There have been minimal randomized studies addressing best practices for insulin use, particularly in non-research settings, where systems are not ideal for insulin management. And this is both on the inpatient and even on the outpatient side.

With that in mind, how do we actually do? Well, I would suggest that this is really an organized chaos. Let me explain. This is one retrospective look on how we do with over 2,900 patients with known diabetes or diagnosed hyperglycemia during a three-year review at a tertiary care hospital, an elderly population, age of 69 years on average, length of stay, almost six days. And what do we see? We see in

the first 24 hours, 25 percent of patients had mean glucose levels above 200 -- not TDC. What we see is that for the entire hospitalization, 20 percent had sustained hyperglycemia, mean hyperglycemia above 200. And amazing to me, in the 24 hours before discharge, 21 percent, more than 1 in 5 with mean sustained hyperglycemia greater than 200, with some with average glucose levels above 300 in the 24 hours before discharge. I don't think anybody in this room would argue that this is too high.

As far as hypoglycemia is concerned, only less than 1 percent of bedside measurements were less than 60, and less than 0.2 percent of bedside measurements were measured less than 40, with most of us called now severe hypoglycemia. The point being, we've heard a lot today about hypoglycemia, but at least in this look-back, hypoglycemia was actually quite rare.

Another study of 37 academic medical centers in 2004 with 1,700 eligible adults with 79 percent with known diagnoses of diabetes, over half on outpatient insulin therapy, and at the time based on

the Leuven study, the ICU target was less than 110 milligrams per deciliter. And taking a look back, what was shown that almost a quarter were in the ICU on day 1, 14 percent in the ICU on day 3. And what you can see is looking at those within target, which again was less than or equal to 110, it was quite rare, either with diabetes or without diabetes, both on days 2 and days 3. And what we see is percent of ICU patients hyperglycemic. Now, here it is quite common; whereas what we see here is on day 1, 2 and 3, hyperglycemia is actually over 70, 80 percent with SubQ insulin. IV insulin is better, but around half of patients if not more than half of the patients on each day, are hyperglycemic with glucose levels above 180.

So the blood sugar levels are not controlled, no matter how they receive their insulin, although IV did a bit better.

And then if we look at non-ICU patients, they even did worse, whether on IV or SubQ. There was only a statistical difference on day 2, as you can see, but here we are talking about anywhere from 60 to

even over 80 percent of patients with hyperglycemia in the hospital in this very large study.

Other measures, severe hypoglycemia. In this study, the find is less than 50 milligrams per deciliter, less than 3 percent of all patients days. A1C assessment for diabetic patients or less than 30 days prior than admission -- only about a third of patients had their A1C no. Glucose measurements, within eight hours of admission. And remember, over half these patients were on insulin. Seventy-seven percent of patients had their glucose levels measured, meaning 23 percent of patients did not have a finger stick glucose. And then as far as recommended physiologic insulin therapy, which would either be basal bolus therapy or IV therapy for those patients NPO, it was a little under half for the whole population, but a dramatic range based on the hospital, anywhere from 12 to 77 percent. So huge ranges.

So to summarize these data, persistent hyperglycemia with rare hypoglycemia in this large population. IV insulin was underutilized, and in fact

less than half of ICU patients who were NPO received IV insulin. And IV insulin was associated with somewhat improved blood glucose control. There was a wide variation in hospital performance of current recommended diabetes care measures. And so the question then comes, at least we don't order sliding scale insulin in the hospital any longer. Right? Wrong. We go back and look at the data, looking at a review of insulin management in a large Boston teaching hospital. Well, maybe this sliding scale data is only valid in Boston. Let's take a look.

Forty-three percent of patients had basal insulin ordered. Four percent of patients had scheduled mealtime insulin -- four percent. Ninety percent of patients in Boston received sliding scale insulin; 47 percent with some basal insulin, 39 percent with oral hypoglycemic agents; and 23 percent received sliding scale insulin only with no scheduled insulin. Sliding scale insulin alone was associated with a 20 milligram per deciliter risk of more hyperglycemia.

So reviewing the literature, what is clear

is that prior to NICE-SUGAR, the problem was not hypoglycemia, but non-aggressive treatment of hypoglycemia. Recommended targets have made for great academic debates, but do not represent what's happening out in the real world. The problem has never been, we've been overaggressive with our insulin protocols, as we are talking about this morning, but rather as a medical community we've been nonchalant with treating the severe hyperglycemia that is pervasive in our hospitals.

Despite the fact we've been using insulin for almost 90 years now, we don't use it intelligently in the hospital. And is it even possible to improve glucose control in the hospital? Well, there are many possible strategies to have a successful glycemic management program. Numerous IV and SubQ protocols have been published with reasonable to good levels of success. Rich showed some of those protocols. There was no necessarily right way or wrong way to use insulin in the hospital, if a protocol at that hospital is shown to be efficacious and safe. Example: What I want to show you now is a little bit

of what we've done at the University of Washington Medical Center over the last few years with our inpatient diabetes therapy. Keys to success is agreement between all clinicians and stakeholders to glycemic targets and general philosophies of insulin use. And I can't emphasize that enough -- education with the staff, communication between the staff, and examination for the staff for continued improvement -- a champion for each specialty to address questions and concerns, very important -- and an appropriate culture to prioritize and standardize glycemic control.

The culture of inpatient diabetes management at the University of Washington, I feel is quite important. Here is a picture of Seattle with some of the other various landmarks. And here is the University of Washington Medical Center here. And this is why our culture is so important. Parking is very difficult at our hospital, so we make the surgeons park right here. Tony, this is for you.

So this is our story. In 1992, we had an initiation of an IV insulin protocol throughout the hospital due to several near misses with the use of

SubQ insulin, mostly sliding scale insulin. Consider that this was before any controversy of TGC in the hospital. Consider that this was before the introduction of insulin analogs. In fact, it was before the introduction of Metformin. This in fact, more than anything else, changed our culture of insulin therapy in the hospital.

More history. In 2001 to 2002, we had over six IV protocols and no SubQ protocol. So what we decided to do was to standardize all of the insulin orders. The Vandenberg SICU targets from 2001 seemed too ambitious for us at the time, especially in the non-ICU areas. So what we did was we targeted 180 milligrams per deciliter, with implementation of the IV in the first part of the decade, and then in 2003 to 2004, we implemented a subcutaneous protocol. And what we learned and what we did comparing the older protocol on IV insulin to the newer one, was that our newer IV protocol had to take into account the rate of change of glucose similar to what the beta cell is supposed to do when it works, as we felt this would reduce the rate of hypoglycemia.

So as an example, suppose a patient had a glucose of 180 milligrams per deciliter, and one hour alter the glucose went down to 110. Well, this is a big drop, and in our column method that we use at the University of Washington, the recommendation would be to go from four units an hour to 1.5 units per hour. But since this was such a big drop, what we instead put in the protocol for the nurses to do is to go down to the less aggressive protocol, the more conservative column. So we go from column 3 to column 2, and instead of having 1.5 units per hour in this example, the patient would receive 1.0 units per hour. Again, this is all with bedside glucose monitoring on the floor or in the ICU using our currently available meters.

How did we do? Well, we went back and took a look. We looked at 105 subjects, 8 percent of them with Type 1 diabetes admitted to the hospital, mostly all NPO, both medical and surgical. Fifty used our new column protocol, 55 used our older protocol. The populations otherwise were identical. And as you can see, we had a dramatic reduction of hyperglycemia,

both in the ICU -- that is critical care, or the non-ICU side. And we also saw less hypoglycemia, down under 5 percent, both with the ICU and the non-ICU side.

What about subcutaneous insulin? Well, this is a ? I think a much more difficult problem, especially once one gets outside of the ICU setting. Because there's little data in terms of efficacy, safety, or outcome. Philosophies of insulin therapy or disparate, even amongst those of us who are considered experts. What allowed us to standardize our approach in thinking, at least in my opinion more than anything else, was the introduction of basal insulin analogs, because it allowed us as clinicians and eventually as patients, to think about different components of insulin therapy with basal bolus insulin, which really was not possible in the NPH days, because there we were using the NPH insulin both for basal and prandial needs.

So this is what we developed in 2004,where you could see the resident could check off when the glucose levels were monitored. And by the way, as an

attending physician after 20 years, I have never written an order at my own hospital because I'm not allowed. That is a true statement. We have these different goals, both in terms of pre-meal and in terms of bedtime. Notice that the bedtime range is a little higher. And notice we have breakfast, lunch and dinner. We have nutritional orders, we have basal orders, and the resident can just fill in the number of units for basal for prandial insulin. But more importantly than anything else, is it taught an entire generation of young physicians how to think about insulin. And never in my wildest dreams did I think that something that we put as a tool to help patients in the hospital for their diabetes would actually be the most important tool to teach people how to think about insulin, both on the inpatient side and on the outpatient side.

We had correction dose insulin, both with low algorithms based on their insulin dose, medium algorithms, we had high algorithms, we could make individual algorithms. I should point out very quickly that I attend every July, and I'm here in the

first or second week of July and I have a fourth year medical student telling me that Mrs. Smith on the fifth floor is on 20 units of basal insulin with prandial insulin at 10, 10 and 12 on medium dose correction. And I'm sitting there and I'm just smiling, because she gets it. The medical student gets it. And that's how I know we've done a good job.

Strengths and weaknesses of our protocol. Well, we have a few strengths. We have found it to be effective and safe. Standardized protocols ensure best practices for all, and it teaches all involved in patient care how to think about insulin therapy. But we have many weaknesses. It's difficult to keep ongoing teaching momentum about TGC once our diabetes clinic moved offsite. Not particularly effective with high-dose IV steroids. And we have three teaching hospitals at the University of Washington; therefore, we have three cultures. And therefore, the residents and the students are getting three messages. Even the fellows are getting three messages on what's the right way to do this.

So are these protocols that I showed you as

good as computerized algorithms? Well, there actually is one study that looked at this. We were not part of this study, unfortunately. This comes from Glucommander, and this was published in abstract form, comparing this computerized protocol to a column protocol. Truth be known, it was the University of Washington protocol. And the name of this computerized algorithm is Glucommander. And what you can see is that they did a little bit better with Glucommander than our column protocol, and they also did a little bit better with an average of 117 for the column protocol versus 103 for the computerized protocol. How clinically significant that is, I don't know. But I think we did okay, at least in this particular multi- centered trial, which as I understand is still not published. Looking at hypoglycemia, there was no difference, whether it's 60 or 40. The Glucommander did do better with hyperglycemia above 200.

So my take is that we are unique. We had a ten-year head start all because of several near-misses. Our small successes need to be tempered by the

realities of the need to educate a constant turnover of physicians and nurses. What we do not necessarily do well, high-dose steroids in patients eating on the floor, transitioning off of IV insulin, and then a big issue, discharging patients new to insulin into the community.

Computerized algorithms should do better than paper algorithms in most settings. The key is the frequency of glucose testing and the knowledge of the nurse operating the insulin drip. What we are doing now is we have recently changed our IV protocol so that all three of our teaching hospitals; that is, the VA, Harbor View Medical Center and the University of Washington Medical Center, we are all using the same IV algorithms. It standardizes patient care, it standardizes philosophy and culture of insulin use, especially with the residents.

And this is really interesting. In talking about what our target should be, the physician can check, either 100 to 140 or 100 to 180. And I'm sitting in this room last July arguing with surgeons, especially neurosurgeons, that 110 should be the

lowest on our target. And the surgeons are telling me that I'm not being aggressive enough with the glucose. I never thought I'd live to see the day. But that's where we are. Our non-ICU targets are 100 to 180. And we use separate protocols for inside of the operating room and we need higher dose insulin, especially for patients on steroids.

So in summary, our current practices of TGC in the hospital is that despite the concerns about hypoglycemia, the real problem in the United States in the hospital remains untreated hyperglycemia, both in the ICU and on the floors. Despite controversy about actual targets, the real enemy is lack of attention to glycemia in general and intimidation of insulin use due to lack of training, and new concerns about hypoglycemia. So thank you very much, and I'd be happy to take any questions.

DR. MESOTTEN: Thank you for a nice presentation. Dieter Mesotten from Leuven. I do have a little bit of a problem. Tight glycemic control, you defined as somewhere between 100 and 180, which I think is not really tight and you're reading an awful

lot of hyperglycemia when you have these loose targets from 100 to 180, or 100 to 140 in the ICU. Because even we see in patients that have levels between let's say 150 and 170, they've got a much higher risk of dying compared to patients that have even moderate blood glucose control.

DR. HIRSCH: Your point is well taken. What we really have here is a problem with nomenclature. Because if you go around the United States ? and maybe it's different in the EU -- but when you look at the data how things are, especially in the ICU, what you see is that most people are above 180 and in fact most people are above 200. And so if you go back and become more academic and look at tight glycemic control as 80 to 110, out in the real world when we're seeing patients, at least in the United States, the recommendations from ACE and the ADA that came out last year where we say, the target should be less than 180, and we can go down to 110 -- I think for right now with how we do in general looking at where our baseline is, I actually think that's pretty reasonable.

I think if we really try to get, like you said, to the tight glycemic control of 80 to 110, whether it's in the ICU or on the floor where we don't' have the data, I just don't think that's realistic with our current tools, and more importantly, getting outside of the tools for a moment, just with the current understanding of how to do this and the understanding of insulin and the issues with frequency of glucose monitoring. I just think it's too difficult.

DR. MESOTTEN: That is my opinion. We first have to improve our methodological techniques in order to do proper trials, comparing it to media targets versus the high and strict tight glycemic control. I think we have to put more work on how we administer insulin and how we measure the glucose levels, et cetera, how we train our nurses the protocols, et cetera.

DR. HIRSCH: I'm in total agreement.

DR. ANDERSON: Hi, Marcy Anderson from Medical Automation Systems in Charlottesville, Virginia. I just want to thank you and support

everything you just talked about, because I'm in charge of a product called the Roll's Report (ph). We gather de-identified patient data from over 500 different hospitals in the United States, using a particular blood glucose meter that's out there on the market right now. And our data supports yours absolutely. We just saw that in those hospitals with less than 40 milligrams per deciliter, we saw 4.8 percent. In the ICUs that had less than 40.12 percent and the non-ICUs, .36 percent.

DR. HIRSCH: Can I ask your N, your denominator for that?

DR. ANDERSON: 50 million.

DR. HIRSCH: 50, 5-0?

DR. ANDERSON: Yes.

DR. HIRSCH: 50 million.

DR. ANDERSON: Yes.

DR. HIRSCH: Okay.

DR. ANDERSON: That's for 2009. This was actually 2008 data, so for all tests we had 29 million ICU tests, 7.6 million and non-ICU, 22.08 million. We aca5tulaly did a poster on this for Dr. Klonoff's

diabetes technology meeting back in November. We're in the process of doing a paper for the 2009 results. And yes, we're seeing a high percentage over that 180, over that 200 milligrams per deciliter. We're still seeing 25 percent of those patients are in that hyper range.

DR. HIRSCH: Correct.

DR. ANDERSON: So again, we're seeing hyper is still a major problem. The hypo isn't nearly as much of a problem as we anticipated. And for averages, we're seeing in the 160s range for ICUs down into the low 150s. That's a median for all of these different hospitals. And again, they're different sizes, different shapes and focus across the U.S. But just want --

DR. HIRSCH: I appreciate your comments. Thank you very much. Last question before lunch.

DR. KLONOFF: Irl, David Klonoff, Mills-Peninsula Health Services. What type of blood glucose monitoring systems are you using? Do you think that current blood glucose monitors with the accuracy that they have are sufficient for the type of results

you're getting, or if not, how much better do you think they need to get?

DR. HIRSCH: Well, thank you for your question. The answer is, what our hospital is using right now is we are using the Roche AccuChek system. Do I think they're accurate enough? I'd like to see it more accurate. Tony's point I think is very good, looking what he's done down the highway from us in Portland. My issue is, I'm always putting up the flags, getting back to something that was discussed yesterday and I was not here yesterday ? the issue of the GDH/PQQ. Because there are little pockets in the hospital, that as much as I try to make sure that there are no problems, sometimes problems can exist. I intercepted one a few weeks ago, for example, in the cath lab, where I had a peritoneal dialysis patient going in there and it was not on their radar.

So it's continued education about that particular issue with interferences. We are probably always going to have to do education. But to your specific point about accuracy -- independent of the interferences, I would definitely like to see better

accuracy. This 20 percent issue, especially for the number of insulin-sensitive Type 1 patients who come in, where they are sensitive to one and two units of insulin, making potentially huge differences in their glucose, much more of a concern for me in a hospital that we see more Type 1 patients than any hospital in the State of Washington than in the more resistant Type 2 patients where relatively small differences in insulin are not going to have a big impact on outcome.

DR. KLONOFF: Have you seen any data that would let you select a target that you'd like to see for accuracy, like 15 percent, 10 percent, any number?

DR. HIRSCH: I mean, the lower the better. Where the issue comes in, quite frankly as I understand it, has to do with how long does the test take and how costly are the strips going to be. To answer one of the initial questions that I raised at the beginning, is cost right now an issue in the hospital in particular when we do strips? To my knowledge, it's not an issue at all, but what is an issue is the time it takes to do the test, because the time of the nurse now becomes a real issue. Because

that's much more costly than the strip itself, and nobody thinks about the time it takes the nurse to do the finger stick glucose. And so if we get an accuracy down, let's say 5 percent but it takes 5 minutes to do it, I'm not sure it's worth. So there's all these things that have to be retaken into consideration.

DR. KLONOFF: That's really difficult, because one of the trade-offs that the glucose monitoring companies might have to use is a longer time for the measurement to get more accurate.

DR. HIRSCH: And that's going to be the problem. That's where the rubber's going to really hit the road.

DR. KLONOFF: That was a great presentation, as always. Thanks, Irl.

DR. HIRSCH: Thank you. Okay. That ends our morning Session 3. I thank you very much. It is now lunchtime. We will meet back here for the Panel discussion at 1:30. Enjoy your lunch.

(Recess for lunch)

DR. HIRSCH: So we're still waiting for a

few of the panel members. Is Dr. Rollins still here or did he leave? Dr. Rollins left. Oh so -- okay, okay. So it's -- it's a smaller panel, and we are in stereo. Before we start, I want to introduce Dr. Patricia Beaston who is joining our panel. She's a medical officer at the FDA and a graduate of the Medical College of Pennsylvania, and welcome to the panel. And I think what I'd like to do -- I think we've all had some very stimulating conversation at lunch about what we heard this morning and before opening this up for full discussion, I'm going to put somebody on the spot here. And in particular, I'm going to ask Dr. Beaston who heard everything this morning and I know I heard at lunch with my own ears you had some interesting comments about what was said this morning. I'm curious -- what are your sort of top level thoughts and specific concerns you may have had about what you heard this morning?

DR. BEASTON: Well I guess, one of the main concerns is there doesn't seem to be a consistent agreement on what is tight glycemic control. I mean, is it normal glycemia? Is it better than what we've

been doing? You know, what -- what are the goals? And that will help inform the needs for performance of whatever we use for glucose monitoring based on what the levels of glycemic control are. The other is that there doesn't seem to be a consistent use of the definition of hypoglycemia whenever trials are done. Some use 70, some use 60, some use 50. So I think it's important if people want to be able to compare trial to trial and end points that there's some consistency. Certainly they can use other targets, but there should be some approach that makes it easier for people to compare outcomes. And the -- another is the concept of time to get a reasonable result. So I understand that nurses are really busy. I understand that you don't want to have to wait five or ten minutes to get a great result. But if you're trading five or ten seconds for a minute but you're going from a 20 percent error to a five percent error, is that not a reasonable exchange? One of my favorite things that I was always reminded of is, if you don't have time to do it right the first time, how do you have time to do it over? So if you're not reasonably

assured that the glucose level that you're making your management decisions on is any good and you're spending time repeating it or you got it wrong and now you have to go find the D50, or you have to treat the patient otherwise for the severe hypoglycemia, what's the trade off for that time? So there's a bunch of clinical issues that sort of go into how you're going to figure this all out that people really haven't discussed too much that I'd like to hear about.

DR. HIRSCH: Okay. So there were -- there were three topics and I think two of them -- the first two, we can separate from the last one in that part of what we are talking about is nomenclature when we talk about tight glucose control in the hospital. We are talking about definitions and what we -- what I showed you, what we do at our hospital -- we don't call it tight glucose control or tight glycemic control. That's just sort of what the literature calls it, and it's almost taken on a life of its own with all of the inpatient studies. But I actually think your point is very well taken. We don't have a good definition of it. And it's sort of like anything. When we talk

about a topic, we need to make sure we are all talking about the same thing. And this is probably -- and again, I agree with your comment -- no more as important if mostly important for the topic of hypoglycemia. A few years ago the American Diabetes Association came up with a biochemical definition of hypoglycemia which is less than 70 milligrams per deciliter, which is different than the accepted definition of severe hypoglycemia on the outpatient side which is requiring the assistance of another person which is very different than something that on our AACE-ADA committee we could not find where the definition of severe hypoglycemia in the ICU being less than 40. We could not find where that actually originated from. And -- and it almost seems to me, and I'd be curious what other people think, that the first thing that we need to do as a group is come up with a set of agreed upon definitions. Because right now, our definitions for these topics are just not consistent. Not only between societies and between disciplines, but maybe more importantly between hospitals at the patient level. I'm curious if anybody

has any other comments on that point. Either in the audience or -- yeah, go ahead.

DR. MESOTTEN: I do have some comments. I mean when we talk about tight glycemic control, we have to back to all the clinical trials that have been done. So three in Leuven, the NICE-SUGAR trial, VICEP, GLUCONTROL. I mean they all had an intervention group 80 to 110. So I think when we're talking about tight glycemic control -- tight -- I'm not a native English speaker but tight means "very narrow." I mean that's 80 to 110. I mean other types are intermediate or no glucose control. But when we're talking about tight -- whether it's good or bad, I mean that's a different issue. But that's very narrow, 80 to 110, looking at the lowest risk association in a J-shape curve.

DR. HIRSCH: So, so, you would agree though that no matter what we decide we all need to be in agreement, whatever it is. Okay. So then my next question coming back from this morning -- I mean we looked at some of the U.S. data in terms of how we do with control, and the answer is not very well. What is your impression in terms of tight glycemic control

in the EU or even in your country? Do you guys do better than we do?

DR. MESOTTEN: I don't want to go into a comparison versus USA because it always -- politically incorrect to do.

DR. HIRSCH: Smart man.

DR. MESOTTEN: I mean we definitely in favor of tight glycemic control and we still do it in all our patients. I mean, I often go around the country and see many, many colleagues in Belgium and Netherlands, and namely also Germany. Most of them, they use a modified version of tight glycemic control and what they do -- they bring the upper limit of the tight glycemic control range to about 140, 150. But they leave the lower limit to about 80. So they would never, ever tolerate 180 because that's the level we will tolerate for general hospitalized patients, where you only measure like twice a day maybe. But in the ICU I think we should be able to do better. If you look at the J-Shape curve. If you tolerate levels up to 150-160, you significantly impair patient survival.

DR. HIRSCH: So I want to make sure that I

understand that correctly. You will measure it twice a day even for somebody receiving four shots a day in the hospital -- not in the ICU, but in the hospital?

DR. MESOTTEN: Clinical practice learns that that's the case, yes. And I agree that that's not appropriate to do. But, I mean, if you're on a surgical ward, surgeons -- they are not really interested in glycemic control, and they don't take the proper measures to do control.

DR. HIRSCH: Hear that Dr. Furnary?

DR. FURNARY: I was waiting for an opening.

DR. HIRSCH: Okay.

DR. FURNARY: So -- and I moved closer so that I -- because I don't have a microphone, but -- I think, first of all, surgeons in this country -- this country is different than Europe. Actually Europe, I think the data show, have tighter glycemic control than we do. The mass data shows that our average tight glycemic control in this United States has an average of about 161 the last I looked at it, and in Europe it's definitely lower than that. I think it's in the 140s or 130s. The important part about tight glycemic

control to define what Arleen was -- or what -- I'm sorry, Patricia, was asking about was that one has to look at what outcome measure you want to improve. If you just want to eliminate infection, all the data shows -- there is no data that does not show -- that 150 is better than 180. You just have to be below 180 because all the biochemical and physiologic things that affect the immune system kick in at 10 millimolar or 180. If you want to affect mortality, you need to at least be below 150 and according to the J-shaped curves you need to be between 80 and 120. If you want to affect transfusion, our data shows -- and I think Reeds (ph) also shows you need to be less than 140 if you want to reduce transfusion. Our data shows that if you want to reduce arrhythmia, we haven't found a low end to that and that's why we're at 70 to 110 because arrhythmia is almost non-existent in our population now and the deaths that we prevent, half are prevented from the elimination of arrhythmias and half are prevented from the elimination from heart failure. So how tight is tight? I think the -- it depends on the patient population and the outcome

you're asking about. So -- and that answer is scientifically out there in the literature.

DR. HIRSCH: Tony, I think to your point, Mercedes Falciglia from the University of Cincinnati actually looked at a very large population of vets showing that the glucose control -- whatever you consider tight -- is dependent on their primary diagnosis.

DR. FURNARY: So --

DR. HIRSCH: And there are some diagnoses that it didn't make a difference and that's -- that's important too.

DR. FURNARY: Yeah, it's a really interesting piece. And, you know, I didn't get into it earlier today but in my mind there are actually -- it's why I - - there are actually six different things that affect glycemic control. And only one of them is the meter. It's the meter, the pump, the thing that delivers the insulin, the person -- the protocol, the person that interacts with the protocol, and the patient. Every single one of them affects how well we do glycemic control, the rate of hypoglycemia, the

outcome. It's one of the reasons that -- I mean, there are some isolated heart surgery populations that we've shown no improvement in mortality but a huge improvement in infection. So each patient population is different in terms of tight glycemic control. But not as it pertains to this meeting. Not different in terms of how we measure glucose.

DR. HIRSCH: So, hold that thought because getting back to how we started this conversation and the definition of tight glycemic control -- and it is relevant as far as meter accuracy is concerned. From what I'm hearing from all of our discussion, is it possible that tight glycemic control is dependent on the population being discussed and so there for those numbers also potentially could vary based on the diagnosis of that patient?

DR. FURNARY: Yeah, that's made exceedingly evident in the VICEP trial. Septic patients have a very high susceptibility -- and Dieter can comment on it, so can Richard -- very high susceptibility to hypoglycemia. Cardiac surgery patients not so much. And so I think the patient population really matters.

And so we now have one -- you know, the Portland Protocol has six different target levels because we don't believe everybody should be at the same target level which is a whole different discussion, but one of our target levels is for sepsis. And our sepsis target level is 130 to 165 because septic patients are more susceptible to hypoglycemia. So the answer to your question is yes.

DR. HIRSCH: So -- and this gets back to what Rich is doing with the ADA and the Professional Practice Committee on the outpatient side with ACCORD (ph), with what we're learning with long-standing Type I Diabetes -- is it -- are we sophisticated enough as a medical community to have different targets? Whether it's A1C on the outpatient side or glucose on the inpatient side to have different targets for different populations? Because I haven't seen that we've been able to do that very well on the outpatient side.

DR. FURNARY: Well, we have it in our hospital.

DR. HIRSCH: You do?

DR. FURNARY: Our cardiac unit is the only unit that's 70 to 110. Our ICU is 80 to 120 and our floor is 100 to 150. And we do it on the floor which is a huge -- we can get into that. We, like you, have done it on the floor since 1995. Insulin drips -- on the floor -- point of care meters. Hypoglycemia less than -- in the floor 100 to 150 -- less than two percent. So yes, you can have different target ranges, but you have to have the same protocol. I think when there's six different protocols and they're all written differently and people aren't familiar with them, that's a problem.

DR. HIRSCH: I want to ask other people on the panel -- do you think we can have -- in any given hospital; can we define tight glycemic control differently? Not so much based on the ward, but based on the -- or where they are in the hospital -- but based on the diagnosis. I mean is that something that you think we can do? Trish -- Rich.

DR. BERGENSTAL: Well, I mean I think this is the perfect discussion. This is what we need and I don't know if we'll solve it today, but this will be

the going home work, I think, for panels of people to do. Because I was initially thinking, "Well, can we just say ICU versus floor? Can we say -- optimal is 80 to 110 and current target 110 to 140 and acceptable under 180, but then it's different from the -- now I'm hearing it's not just the unit and the floor, but it's the patient type on each of those. So, I hope we could sort that out. I mean, as you say, we're struggling with that on the outpatient side. We get criticized to say, "Oh, you say less than seven for everybody. That's not safe." Well, let us tell you who the people that it's not safe for and make an exception, but don't treat everybody to less than eight just because there's ten percent who shouldn't be less than seven. So I like this discussion. I don't have the answer today.

DR. HIRSCH: Go ahead, Patricia.

DR. BEASTON: Well, during my fellowship I took care of a lot of transplant patients. I took care of liver transplant patients, and cardiac transplant patients, and renal transplant patients. They were all different patients. And you had to not

only figure out what kind of transplant they had, where were they on their immuno-suppressant regimen, were they getting fed, were they not getting fed. I mean, it gets to be very complicated. So, for people who do this all the time, you really can get into tune with what individual patients need. And I think it's reasonable to have flexible algorithm that goes through a certain process, but that the physician who is in charge of that patient can say, "For this patient, given his or her history and these medications, this is what I think is appropriate for them at this time." With the understanding that if something changes you need to be made aware because that algorithm can be drastically changed. I can't tell you how many times they changed the immuno-suppressant drug and then didn't notify the endocrine service and then the patient got into trouble. So, you -- it's not a one-size fits all, but I think that there's a process by which you can take everybody through that they'll be comfortable with the process and have enough flexibility that they can follow what those instructions should be for that patient.

DR. HIRSCH: Go ahead, Dieter.

DR. MESOTTEN: I would strongly disagree with certain opinions. I mean first of all, I think we should think scientifically first. There's a difference between randomized clinical trials and implementation studies. And I think from implementation studies, we cannot delineate different operations that would -- may require different target ranges. When we're talking about, for example, the VICEP trial, overall the study was under power to detect a difference at all. So you cannot draw any conclusions out of it then say like, "Okay, in septic patients, we'll have to use different target." I mean these are non-evidence based statements that you have to use something intermediate. For example, if you take the NICE-SUGAR trial and you say, "Okay, I believe the other." Then you should stick to 144 to 180 mg/dl. There's no evidence to go for somewhere in between 120 to 140. And from a general point of view, I think it's very dangerous to go back to the years but every physician will decide, For this patient, I think this one is the best. I mean we have to take

into account evidence-based medicine and it's different trials. And nothing that you can decide for your patients is the best it's going to be. I mean, for example, if you compare it to the airline industry -- I mean you've got different airplanes at different airports, etc. They've got very much standard operating procedures and it works really well. There's definitely a need for standardization and not go back to different targets, different techniques, different protocols. It really confuses people. And that's the difference between the

Leuven studies where everything was basically standardized, and all the confirmation multi-center trials where everyone was let free and there was no standardization at all. I think that we should stick to one target, get our nurses used to it, work with one protocol, one type of infusion, one type to measure blood glucose levels, to improve outcome. And that's the way to go. And I think there's an awful lot of work to be done on the methodological side -- point of view: measurement, protocols, etc. But we should really think scientifically, and a

randomized trial is much stronger than implementation studies.

DR. HIRSCH: Okay, go ahead Courtney. You're itching here.

DR. HARPER: Well, I just want to actually thank everyone for this particular discussion -- both this morning in the presentations and now. Because it highlights the importance of, I think, delineating what is needed in this area and evidence that base medicine is obviously the highest bar. But it also highlights some of the maybe non-consensus in the area about what to do, which -- you know, so this discussion is good and hopefully maybe one outcome of this meeting is that there will be some efforts to move forward and maybe to find some of these terms could help first, and then some of these things. The reality for us, though, is that we're being faced right now with situations where we're being asked what studies are necessary to show that my device can be useful for this. And whether they be a blood glucose meter or some other type of technology, you know, we would like any input that we could get as to how we

can actually try and demonstrate the performance at a level that's necessary for this patient population and this use. So -- so I also encourage you all to think about that and if you have some input today we'd love to hear it, and if you want to talk with us further, we'd love to actually hear from people and their opinions on what types of studies are really needed here.

DR. HIRSCH: Ms. Mann, you've been very patient.

DR. BEASTON: I'm sorry -- I just wanted to respond to Dieter one second. I mean, airports do have protocols. But I can assure you that you cannot land a 747 on the same runway that you can land a commuter plane. I mean, so there is flexibility within what the needs are for any situation. And to say that everybody is going to fit in a box, I think is also a mistake because patients can come to harm when you make assumptions that any patient is represented by whatever clinical trial that you did.

DR. HIRSCH: Thank -- thank you. Go ahead.

MS. MANN: Elizabeth Mann from the Army Burn

Center again. I've been building up, so give me a minute because there's a couple points that are really important here. I think the issue about individual patient targets is exactly right. I think different patient populations definitely need different targets, and I believe that some of the work done on diabetics - - acute and chronic diabetics or in the acute setting - - they probably need a little bit higher target because physiologically they're used to living at a higher target. How do you do that? Well, we have just been working with a computer decision support system. And I also believe that it's certainly within the realm of possibility today to program those for a diabetic patient, for a burns patient, for a TBI patient, for different populations that the provider can select. The computer does all the work. The nurse isn't bogged down with, you know, multiple -- several column protocols that they have to weed through. And those do get very complicated. The more complicated the protocol, the better it works, the harder it is for nursing. And I'm a nurse so, that's one of the things we do. So that being said,

what is the best target -- is 80 to 110 really realistic? What we discovered in our work and discovering the glucometer error, is that when you have an anemic patient and they're at 80 to 110 but their hematocrit is 20, which is the ABEAR (ph) target -- 21 percent, which is half of normal, they're really sitting at a glucose of 60/65 to 90/95. We're forcing them into that with this tight glucose control. So what are the counter-regulatory mechanisms that get activated when you force a patient using I.V. insulin into that range? It causes more variability, they start spiking, you give them more insulin, they start dropping and you create a vicious cycle. And what we've observed and published is that when we did the mathematical correction for hematocrit, we stopped having the occult hypoglycemia, we stopped having that variability and it was a lot easier to control the patients. So that's one, I think, very valid point that the accuracy of the glucometer is absolutely essential to safe, tight control -- whatever you prescribe.

DR. HIRSCH: So let me ask you a question.

And this is critical. Going back to point number three from Patricia earlier. Would you be willing for one set of patients where you are trying for normal or near normal glycemia -- would you be willing to use a more expensive strip that took up to three, maybe five minutes, for that population, but for another population where you are not trying for that tight of control, using a different meter with different accuracy, maybe closer to what we are using today? Would you be willing to do that?

MS. MANN: With all due respect, I've tested all five glucometers available, personally. The new four channel glucometer is almost identical to the reliability in the lab and that one takes, I think, seven seconds. Ten seconds? Six seconds. Okay, there's no extra time. There's no need to develop a better mousetrap because it already does exist. Our hospital has made the executive decision to change to that technology, but in the mean time we -- in the Burn Center, continue to use the mathematical correction. I re-looked at my data from our published paper. When you use any of the big four

glucometers that are available, you can correct them at the point of care and get within less than ten percent error at every hematocrit level, and in fact at the very low hematocrit levels, the accuracy is less than eight percent. So, we can do it now and there's no extra cost, there's no extra time, there's no extra investment. And that's the bandstand that I keep -- or soapbox I'm jumping up and down on today is that the technology is there. Whether this one company can produce enough glucometers for the entire United States -- now I don't think so. So, there needs to be some intermediate thing.

DR. HIRSCH: Okay.

MS. MANN: And then -- oh -- should I say it out loud? It's the Novasure Stat Strip, which is the four- channel glucometer. And those data we just published in critical care medicine in February that we did in the Burn Center. But I'd also like to say that as far as protocol. It is -- it is -- the glucometer -- and it's been said over and over again -- is the tiny part of tight glycemic control and it depends on the nurse and on the protocol that you're

using. We just did a study that's going to be published on the computer decision support, and in a burn patient who's hypermetabolic, has no liver, no muscle stores, poor glycemic control -- this is a very safe method. And our rate of hypoglycemia, using our regular point of care glucometer that we do correct with hematocrit -- our rate of less than 40 is .1 percent. So it can certainly be done, but I still think that computers are the way to go. You can't standardize among providers and among centers, especially to do a big study that we need, without this type of control. And let the computer -- I mean a computer can land a jet plane -- I think it can help us to guide some therapy based on the patient's response, and tailor it to that individual patient.

DR. BEASTON: I have a question. Are you doing capillary glucoses or are you using the meter and then using venous blood or arterial blood on it?

MS. MANN: We only use arterial and venous blood in the Burn Center. And in the studies that I published, it was always arterial or central blood -- no capillary blood. Anyway, thank you very much -- I

feel strongly about it.

DR. HIRSCH: Okay. Thank you for your comments. So -- so, the question that I have for the whole group is, you're hearing a few opinions. We're curious -- what do we need to have developed that we don't have now? I mean -- or do we have what we need to have developed and we didn't even need to have this meeting developed? Because I don't believe that. But I'm curious, for where we are right now in terms of where we are with our strips and the precision and the accuracy, I'm curious if we can have some discussion on where we need to go with this technology. Please introduce yourself, sir.

MR. SOUTHERLAND: Hey. Phil Southerland. Team Type I, Atlanta, Georgia. So, I agree. Science tells all and a large randomized trial could do a lot for us. It's just what is large randomized trial? So in a "N equals 2" study, I put a continuous glucose monitor on my best friend who does not have diabetes, and then over a five day stretch, I try to mimic my blood sugar to his. So, the question being, could we put a large- scale randomized continuous glucose

monitor study on non-diabetic patients -- people -- and find out what is the norm? What is the goal? Where should we be striving for? And then use this technology, the CGM which I use and have used for the past two and a half years straight, to try and mimic people without diabetes, thus preventing complications that often stem from this disease. Has that been done, and if not, is it something that could be looked into?

DR. HIRSCH: So if we were going to do a CGM study in a hospital, specifically an ICU, what would the -- would the end point always have to be mortality? Could we use other end points?

MR. SOUTHERLAND: I prefer to stay alive, so. . .

DR. HIRSCH: I mean it's important because what we heard today, to do a study powered to show mortality with the sort of blood sugars we're talking about like we're seeing in NICE-SUGAR; if I remember the number it was 70,000 people. So I think one question -- and don't get me wrong, there's probably no bigger CGM proponent in the audience than me right

now, but I'm very concerned that once we start doing CGM studies, prospective, randomized, multi-center studies, we have to be very careful where we set the bars. Because the power to see the mother of all end points -- mortality -- is so high. We would need so many people.

MR. SOUTHERLAND: Well, I mean, could we look to the average among 2,000 people without diabetes say --

DR. HIRSCH: I mean there are other end points than mortality, and specifically I think the big one here we're talking about is hypoglycemia. Why don't we -- why don't --

MR. SOUTHERLAND: Well hypoglycemia, but also to your point and what you say in many of your talks is the standard deviation -- the variability, and find out what does a person without diabetes do, and then can we try to aim for that as a goal.

DR. HIRSCH: Right, but we need to have hard end- points. And looking at statistics and math isn't going to cut it for what we're talking about here.

MR. SOUTHERLAND: Fair enough.

DR. HIRSCH: Why don't we move on? Anybody? Anybody else up here? If not, the surgeon from Portland.

DR. FURNARY: Yeah, I want to address your question. I'm a surgeon from Portland. The question is where do we need to go? What tools do we need? And I'm going to restate, Irl, that I don't think that the focus of this -- these two days, is proof of concept, or disproof, or trying to figure out what target level TGC should be at. And I think linking clinical outcomes to an approval of a CGM or a point of care device is not what the FDA is all about. Now -- Patricia and Courtney --

DR. HARPER: That depends on what somebody claims. So if somebody comes in with a device that says this device is to achieve tight glycemic control in the ICU, then that is what we actually need to show. So. . .

DR. FURNARY: I think that once we get to the closed-loop pancreas -- the artificial external pancreas -- that's the goal, but I don't think that's

a current goal.

DR. HARPER: I'll be -- I'll be -- you know, the artificial pancreas is definitely a great effort, and we're working on that. It's definitely a couple of years away until we get something that is as advanced as that. But there are stages in between that that may come more quickly. And there's also similar products under development that are not necessarily what you would think of as the artificial pancreas, closed-loop, that may come in advance of that. So, you know, this stage-wise approach to get to the point of having these technologies, you know, we may see that sooner. And so we need to figure out, you know, how to do these studies, and what types of end points, and how good does the performance need to be. So, it may be that we don't know that, but it may be that we do. So one question I would have for you is that I've heard a couple of conflicting statements here. So on the one case, I've heard people say, "You know what? We don't need that many measurements. You know, if we have too much data, it doesn't help our algorithms," and things like that. And on the other

hand I've also heard things to say, "If we know the direction of change, and the rate of change, and if we have more measurements, maybe we can be better." So which is it?

DR. FURNARY: It's a -- that's a perfect segue to what I got up to say. And, what I got up to say was I'm going to readdress Dieter -- Dieter's question about whether this can be done with current technology, and what's different about why can Greta do it in Leuven, and why can I do it in Portland, and why can no one else do it? Someone asked that question. And the reason is the frequency of measurement. In Leuven it can't be done with point of care devices because the most frequent that they measure the glucose is every hour when it gets low. And so that -- but in Portland, the protocol says that when you get low you measure every 30 minutes. And what happens is the more frequent you take measurements, it starts to get rid of some of that variability. And so if you have a measurement that's every 15 minutes apart, and it has a 15 percent deviation, that's probably as good as a measurement

that's every minute that has a 20 percent deviation because you're going to start narrowing down. The cluster analysis of what goes on gets you a better reading. The different is -- and the reason hypoglycemia doesn't matter in Portland is because any time we get down there, we're measuring it every 30 minutes and they don't -- the average time in hypoglycemic range is 33 minutes. In Leuven, it can't be less than an hour.

DR. HARPER: Can I get you to clarify one thing?

DR. FURNARY: [Affirmative.]

DR. HARPER: So are you talking solely about an imprecision? So obviously if you measured more frequently, you're going to reduce the impact of imprecision a little bit.

DR. FURNARY: Yes.

DR. HARPER: But are you also talking about a bias, or --

DR. FURNARY: No, I'm talking about imprecision. And so, what I'm saying is, yes, to answer Dieter's question earlier this morning -- and I

left you with this -- is that yes, tight glycemic control can be done with current devices if used frequently enough. Now, do we need -- so what is that -- what about everyone else? Not everybody's going to measure every 30 minutes, or every 15 minutes because it takes a lot of time. This is why we need -- and this is the answer to Irl's question -- where do we need to go? We need to go to continuous glucose monitoring devices. Because continuous information gives us much more information to prevent hypoglycemia and I would rather have a measurement every minute that has a 10 or 12 percent deviation than a measurement every hour that has a five percent deviation -- a five percent MARD. Because I can steer the patient -- we can steer the patient where we want them to go. That's the difference. And so, that really brings us full-circle to where I think the FDA needs to be focusing on, and this is probably the tough question is -- how do you approve a CGM device? My point -- earlier point is, coming back around full-circle, is you don't approve a CGM device based on the outcomes; you approve it based on how good it is at

telling you actually what the blood glucose level is.

DR. HARPER: Right. And so, you know, the types of patients that we need to look at, the values of blood glucose that are most important. I mean I think that we did get some of that information today. But one thing -- you know, some of the things you say make me wonder -- is it -- it still probab -- they need to be equally accurate --

DR. FURNARY: Yes.

DR. HARPER: But it can tolerate more imprecision perhaps -- is that what you're saying?

DR. FURNARY: Probably -- I don't even think you need to tolerate more -- I think they're going to be equally or more accurate. But what I'm saying -- what I'm saying to Dieter to answer the question earlier is, you can use current devices if you use them frequently enough. You get rid of that and make it available to the common man by making it continuous. And it's going to still improve. And most of the continuous devices that I've seen are at least as good as, if not better than, the current POCT devices in terms of MARD.

DR. HIRSCH: Now the one thing, just to be clear, Tony, with the CGM devices -- and I can't speak for the ones in the future, but at least the ones now -- they are dependent on the accuracy of the point of care capillary glucose level. And if that is off by 19 percent, you potentially have a real problem if the MARD is 15 percent on the CGM device.

DR. FURNARY: I think -- and I'm familiar with one, two, three, four, five, six of them. I'm familiar with six of them. And that's a correct statement, but it's only correct if you use a point of care device to get your baseline to basically calibrate the device.

DR. HARPER: All CGMs are currently calibrated with the blood glucose meters.

DR. FURNARY: No. They can be calibrated by a lab measurement. They could be -- you can calibrate them by anything you want to calibrate them by. You can calibrate them by mass spec if you wanted. You can calibrate by anything you want to calibrate with.

DR. HARPER: I was talking about the labeled

performance.

DR. FURNARY: Oh, okay. I don't know the labels --

DR. HIRSCH: We're all into labels here, Tony.

DR. FURNARY: I do agree with you that whatever you calibrate it with, you're going to be limited to that amount of deviation.

DR. HARPER: So do you think the interstitial CGMs are -- are going to be accurate enough for this use, or do you think that you need a whole blood CGM?

DR. FURNARY: I personally believe we probably need a whole blood CGM but because the current interstitial devices that are out there have been out there for what, Irl? Six years now?

DR. HIRSCH: Mmm. . .almost five.

DR. FURNARY: Five? That's pretty good for a surgeon -- I was close.

DR. HIRSCH: You're not a typical surgeon, Tony.

DR. FURNARY: I'm going to park in the bay. [Laughter.] What was the question? [Laughter.] That's a typical surgeon.

DR. HIRSCH: Yeah -- yeah, annual --

DR. FURNARY: No, interstitial device -- and we haven't used them. And I'm taking up too much time because I'm not on the panel.

DR. BERGENSTAL: Irl, I mean I briefly showed you a little bit of data today to say there are some intravenous continuous monitors that I think are early but starting to show that it's possible to do this. I mean, those 19 patients were exposed to -- I think it was 150 different drugs of all types from L-Dopa to Acetaminophen, to -- and they still held up with very good MARDs. So, I mean it's early, it's research. But that's where I think we are headed. To Tony's point that we can get a continuous monitor in the ICU -- don't think we need that on the floor --

DR. HIRSCH: Yeah. And I agree with you because we're dealing with intravascular and not interstitial fluid where you're going to have even more changes in lag and problems and hypotensive,

hemodynamically unstable patient if you are actually in the vessel. The surgeon or the pediatrician?

DR. FURNARY: Well, he said I like to hear myself talk, so since surgeons have big egos, I'll just sit down.

DR. HIRSCH: Okay. Go ahead, next -- next speaker.

DR. GINSBERG: I just wanted to make a comment. A couple of years ago, I presented a paper at the diabetes acknowledgment society talking about partial duplicates, which -- since CGM is a frequent measurement, the values that it gets every five minutes are not independent. That, within reasonable limits, patients don't change blood glucoses very quickly. That if a patient blood glucose is 100 now, it is not going to be 200 -- most of the time -- five minutes from now. In particular, when it's on a continuous infusion. And so therefore, if I get a value now which has an error of 15 percent. And I get another value five minutes from now which has an error of 15 percent. If you assume they're complete duplicates, which they are not, then the error of

those two measurements together is only 11 percent. If they get another measurement five minutes from then, then the error goes down to about nine percent. And after not very many measurements, my error is no longer 15 percent, my error is now six, or seven, or eight percent. Plus I'm getting a trend out there now with the understanding that there are all sorts of problems that you just limited, in terms of hypertension and so on, for continuous systems for patients in which they do work. I'm not sure the lag is all that terrible. A 15 minute lag under these types of circumstances is probably not as bad as we're seeing anyway. And at least it's something to think about in terms of how we use these things. I just wanted to point out the duplicate problem.

DR. HIRSCH: Good point. Good point. Anybody else? Next speak --

DR. WHITE: Neil White from Pediatrics at Washington University. First of all, I want to -- I want to say that I'm very pleased and compliment Dr. Furnary and the other woman here from the Burn Center on how good a job they can do, but I think what we

have to try to figure out is what kind of technology we need so that all the rest of us can come close to doing such a good job. Whatever that job needs to be, whether it's 80 to 110, or 110 to 140, or whatever that is. I'm not going to weigh in there because I have no knowledge in this area other than what I heard people say. But we probably need technology that would enable me, if I were in that boat, to do the same thing that Dr. Furnary can do, which I don't think we can do at most hospitals.

DR. HIRSCH: But -- but one comment to that, Neil. One of the things that Dr. Furnary said wasn't just the issue of the technology; it's the frequency of testing.

DR. WHITE: Well, I think I agree with the point that the more frequent the testing, assuming it's reliable, the closer we'll be -- we'll be able to do this, okay? Continuous glucose monitoring is probably the way to go, but I would have doubts that continuous glucose monitoring of interstitial fluid in the ICU setting would be a way to go. If there's continuous glucose monitoring in the vascular setting,

I think that would be a big step in favor of doing this. And I know there are things being worked on. I mean that would probably be a way to go in that setting. Totally different -- just like meters are totally different -- for the setting of the average diabetic walking around on the street.

DR. HIRSCH: I guess my only point, and I don't know about the IDC in Minneapolis or anywhere else, but the number one complaint that I hear about especially when we start talking about I.V. insulin on the floors, or even sub-Q insulin in somebody on MDI is that the nurses tell us that they don't have the time for the minimal amount of testing we do now. Over and over and over again, that is the complaint because the nurse to patient ratio isn't enough to keep that. And that's just the complaint. We've been able to deal with that somewhat at my institution, but it's tough.

DR. WHITE: What your institution's able to do is admirable. And as you know, I have a lot of experience in the past with I.V. infusions of insulin. But if I try to do what you do at your medical center

at my pediatric hospital, they string me up every other week when I bring it up.

DR. HIRSCH: Go ahead. Do you have any comments?

DR. MESOTTEN: I mean I completely agree with you. I mean, it's maybe true that Dr. Furnary can do tight glycemic control with point of care blood glucose meters when you measure every 30 minutes. But I mean there's ample literature out there saying that -- measuring at least every hour is already very hard for the nurses, and it increased too much of the work load. So, I think we have to improve something about the technology so that we can go to measurements less than one hour and talking about continuous monitoring is not there at the moment, and they still have to prove they have value in the clinical setting. So in the meantime, we have to do something. And there I don't agree. I mean you can say that you measure every 30 minutes, but that's -- in most centers, in Europe and U.S.A., wherever you are, is impossible and definitely not in medium care or the channel ward (ph).

DR. HIRSCH: Thank you. Yes?

MS. KOLLER: Beth Koller from Medicare. I have a question that's more broadly directed toward data sources and probably relates to something that Dr. Beaston or Dr. Harper can answer. At our agency, we frequently have sponsors come in to present about their products. The data maybe -- the sponsor may also be a vendor for that product for durable medical equipment. And the information may be derived through those vending activities. The vendor supplies that informa - - supplies the product to the patient, but the data stream basically appears to be through the sponsor plus or minus the durable medical equipment vendor. And we have some questions as to whether the FDA would accept data if in fact the data were not obtained having gone through an IRB protocol, and if there was no patient consent. And there was not a clear protocol.

DR. HARPER: Our regulations require that studies done on human subjects be done under IRB and under informed consent.

MS. KOLLER: That's not necessarily the

kinds of data that we see. I point that out to show the differences between the two agencies.

DR. FURNARY: I want to come back to a point that Richard said and that was that, you know, this is something that we do in the ICU. I don't disag -- I disagree with that. Glycemic control is not just for patients in the ICU. And our data, as well as the Leuven data, and Irl's data -- there's a number of -- there's a lot of data out there that shows that the length of time that you're hyperglycemic, the length of time is what impacts outcomes. It's not just the target level; it's how long you're there. Same with hypoglycemia -- it's not just how low you go, it's how long you're there. And to limit glycemic control to a patient population that resides in the intensive care unit is to say, "It doesn't matter out there." It would be like giving less than a full course of antibiotics. It's the same thing. We didn't -- antibiotics don't improve infection if you just give them in the ICU -- you give them after the patient leaves the ICU. Because there's a duration of care that matters. Just like

that, the duration of care impacts the outcome and glycemic control. So I believe that glycemic control is something that should be afforded all the patients, including patients on the floor, and that also speaks to why we need a very accurate CGM monitor on the floor so that the nurses aren't continually doing this on the floor, and it doesn't take up all the nursing time. So you asked -- it comes back to the question what do you think we need? That's what I think we need.

DR. BERGENSTAL: All right. And let me just respond, because I hope I didn't imply that -- when I was saying -- yeah, I think we definitely need control on the floor. The question is whether it is 80 to 110, and again I'm coming back to it's just the personnel and the staffing at the moment doesn't make 80 to 110 practical on the floor. We probably are as aggressive as anyplace with the -- what we call our complete insulin orders and the triple orders on the floor with frequent monitoring, but that we can get -- we can get 110 to 150, sort of, on the floor.

DR. FURNARY: Yeah, thank you Richard. I

just wanted to be sure that FDA heard that. That this is -- to me, this is not an ICU ther -- ICU only therapy. And I think --

DR. BERGENSTAL: But that's where that term gets a little -- TGC is sort. . .

DR. FURNARY: It's glycemic control.

DR. BERGENSTAL: I -- yeah, I'm for glyc --

DR. FURNARY: It's glycemic control. Whether you call it tight or strict or intensive.

DR. HIRSCH: You don't want to just call it GC, Tony, that's something else.

DR. FURNARY: Yeah, I don't -- we know what that is.

DR. HIRSCH: Yes. Okay. Go ahead.

MS. COOPER: Hi. My name is Emily Cooper. I'm a clinical nurse specialist at York Hospital in York, Pennsylvania, and we're a small community hospital -- about 550 beds. And I just wanted to give you the perspective of, you know, outside of a university setting. We use Portland protocol. I work with cardio-thoracic surgery patients, and I have to tell you that our biggest barrier to getting tight

control with that protocol is our glucose meter. It has a lower hematocrit threshold of 25 percent, and with the permissive anemia we have with those patients, we have a lot of patients that are below that threshold. And because of the litigation issues described this morning, our institution mandates that if their hematocrit is less than 25 percent, we have to send a whole blood glucose to the lab. So you can only imagine the chaos that ensues, and when they're in the intensive care unit they at least have an A-line that the nurses can draw off of, but still with the lab turnaround time we're not getting --

DR. HIRSCH: What is the lab turnaround?

MS. COOPER: If they're in the unit, we can maybe get it in five or ten minutes for a whole blood glucose, but then like Dr. Furnary said, once they get out to the floor and they no longer have a line, then it's a phlebotomy stick. And we can't run the insulin drips on the floor because of that. And these poor patients are getting stuck eight times a day -- phlebotomy sticks just so we can measure their blood glucoses.

DR. HIRSCH: So --

MS. COOPER: So we obviously need something different --

DR. HIRSCH: Yeah, so --

MS. COOPER: I have to say too, real quickly, our institution -- you know, there's obviously other technologies out there, these lovely four-channel glucometers, but because our current glucometers, you know, on face value, meet ISO criteria, there's no incentive to get new technologies -- especially in this economy.

DR. HIRSCH: So what you are really saying -- to answer the broader question, "What technology do we need?" We need better glucose meters that are accurate in terms of measuring people's glucose who are severely anemic. That's a huge problem. We've heard that several times today.

MS. COOPER: Yes.

DR. HIRSCH: Okay. Thank you for your comments.

MS. COOPER: Thank you.

DR. HIRSCH: We are at -- almost nearing

the end of the session. I get the one minute card here hitting me in the face. Does anybody have any concluding comments that they want to make before we do end the session? I want to -- Patricia, I want to get back to your comment just for a moment about what would be acceptable in terms of the more accurate device, in terms of the amount of time. Because I personally don't know the right answer. I think everybody in the room would like to see more accurate readings in the hospital, both in the ICU and to Tony's point, on the floor. Ideally, we like it to be cheap. We wouldn't like it to take away all the money we have. And by the same token we like it to be fast. But it's a -- you know, as we heard just now from this nurse from Pennsylvania, there is a real problem even dealing with sub-Q insulin when you have to wait an hour at the best, maybe even longer on the floor, if you're dealing with somebody on multiple daily injections, and the meal is there and you have all the normal things that happen. Maybe the patient feels hypoglycemic but isn't. But the nurse can't use the glucose meter at the bedside because of hypoglycemia.

I mean, there's a lot of issues here that we did not come to a consensus on today, and I'm not surprised with that. I personally don't have an answer for you, but I think, to me anyway, that's the most provocative question of this past hour because I really don't know where to even start. Because I think the real answer is often going to be with the administrators and not with clinicians like myself. So, any final comments from anybody before we end this provocative discussion? No? If that's being -- one last comment here.

MR. TORJMAN: Marc Torjman. I'm at Cooper University Hospital. There's one thought that I had and this is from the hospital side, having done a lot of these measurements in ICU patients. I work also with Dr. Phil Dallenger (ph), and I have to say that there are a lot of good meters out there. Good glucometers in major institutions as opposed to maybe small community hospitals, the laboratory directors know about those meters. They're well below the ten percent MARD. I've tested them myself. They perform well compared to a YSI. So, I think that the

frequency of measurement when you're giving I.V. insulin therapy is critical. If you are limiting yourself to one hour measurements, unfortunately that's -- you know what the limitations are because it's an FTE problem. At Cooper, for example, the way Dr. Dallenger does it is when somebody goes on an insulin infusion, the task is helped by a technician. The nurse -- the glucose measurements are taken over by this FTE person that will only do blood glucose measurements. Not everybody can do that, so that's a limitation. But I think the point I'm making here is that I've checked the AccuCheck inform system, the HemoCue when I was at Jefferson for 20 years -- worked with those devices. They're below five percent MARD. So if you can afford those devices, they're out there. The accuracy is out there. The question is, what protocol are you going to follow if you're going to go 80 to 110? A one-hour measurement frequency is just not going to do it and you're going to run the risk of hypoglycemia. So if you push your protocol up to the 140 -- 140 to 180, then perhaps the accuracy becomes less of an issue and you have to really balance out

the frequency. So that's what I wanted say.

DR. HIRSCH: Thank you very much. Okay, with that, I think we will end this session and I thank you all for your attention. We'll move on to the next session.

DR. HARPER: So I'd like to thank all the presenters and moderator for Session 3 for a great session. I think -- I know I learned a lot and I hope that you all did too. It looks like we still have a little work to do in terms of the clinical community to get together so that we can figure out some of these questions, but it sounds like we are well on our way to that. So now it's my pleasure to introduce the next speaker. Ellen Ullman has been a passionate and tireless proponent for diabetes advocacy since 1989 when her 22-year old son was diagnosed with Type I diabetes, and she's going to talk to us today about consumer use of glucose meters and also how consumers choose meters. So, welcome Ellen.

MS. ULLMAN: Well, I see not too many people have left for the airport, so I have more people to address than I thought. I just wanted to

say because it did say in the program that I work for Close Concerns that what I'm presenting today is completely my personal opinion and really is nothing -- is not representative of Close Concerns. So I ran a little survey on the internet. I had about 500 people who completed it, and this is the breakdown of who responded. More women than men, 36 percent had Type I diabetes themselves, 48 percent had a child with Type I, 13 percent had Type II, 3.2 percent had LOTA (ph), and then there were just a few with different aspects -- other areas of diabetes. And 90 percent of the people do have insurance coverage. So if you see the people that I surveyed are actually checking blood sugar quite often. The blue is five to eight times per day, and that's 42 percent, and the goldish color is 8 to 12 times per day. So people are very conscientious. Two to four times per day, 16.6 percent. It was mentioned by Mr. Rollins that for Medicare patients it's required that they get training in how to use their meter. So when asked, "Have you been instructed by a healthcare provider how to use your meter?" 63 percent

said yes and 36 percent said no. So, some people are going home and figuring it out on their own. Control solution -- in my opinion it should be in the box so consumers can choose it because every time you use control solution to compare to see how accurate your meter's functioning, it's really only good as that vial of strips that you're testing. It's not the meter accuracy -- it's that vial of strips. Asking people on average how often they use control solution -- 41 percent say never, 14 percent onetime per year, ten percent four times per year, nine percent two times per year, and then it goes down and 3.3 percent said, "I am not familiar with control solution." I think that when we used to get it on our meters, myself personally, we did use it more often. But now we don't even get it, and we don't have it. It said in this ADA consumer guide that it cost $15 for a bottle of control solution and once you open it, it's only good for 30 days. So, that's a considerable expense for the consumer. So here is a tweet from Twitter: "5 a.m. low. The meter said 79. No way! Help me discovery expired test strips -- lovely.

Control solution had them in range, but in the upper range though." So some people out there are using it. Coding the meter -- have you ever forgotten to change the code on your meter? Well, if people are checking their blood sugar 12 times per day, it's pretty likely that they are going to forget on occasion to code, so 57 percent said yes they have and 31 percent said no. And I guess the others have no code meters. Using strips beyond the expiration date. Have you ever knowingly used blood glucose test strips beyond the expiration date? And almost 20 percent said yes. And I think that we're going to see a lot of more of this -- not that industry can really do anything about it, but given that people are less insured, or underinsured, that they're going to use the strips that they have. And this is a quote that I got in an e-mail from a friend whose son does not have insurance. "If he's using strips, they are outdated ones." Frequency of cleaning skin -- well, this was what was mentioned. How few people actually clean. So 20 percent said that they check -- that they clean every time. And almost 20 percent said very often,

and 11 percent said often, and 6.5 percent said never. So I think, actually, it may be more frequent that we imagined -- at least among this population. And as far as temperature, humidity, high and low -- I asked if they keep a meter and strips in the car. 34 percent do, so then obviously these are exposed to extreme temperatures. 62 percent of the people do not know the temperature range of the meter, and 33 percent do not know the high and low range of the meter. I think it would be really helpful, instead of saying high, flashed 500+, or -20, or less than 20, or less than 30 -- whatever it is that your meter has so that people can make more of an accurate dose decision. Because if they don't know that their meter goes to 500 or 600, they may be overdosing assuming that it's too -- it's even higher than it is. And I'm not going to go through all the other interferences that were already covered. So how many times do people have to use more than one strip? 45 percent of the patients said they sometimes use more than one strip because they do not trust the accuracy of the result.

And again, I just chose some random Tweets: "Test strips for my glucose meter -- you are expensive, that's why you are constantly wrong, making me use more of you than I need." Well, I have to say that I do hear parents very often, and patients very often are retesting. They don't believe it, and although we discuss -- it's been mentioned that they are simply outliers and they're not that frequent, more frequently that you imagine we get results that just don't make sense. And then when we retest, we get a result that seems a little more reasonable. And then here's another person -- it took her five test strips to get enough blood. These are the other factors that we've already discussed. I'm just going to move along. And then I come to how consumers choose meters, or is it really should I ask them how are meters chosen for you? Because, not everybody has a choice today. So the first thing and how do we choose -- the ADA is clearly a reliable source. We get this guide every year -- 2010 -- before they go into comparing, we have a little article on accuracy. How do you determine -- how do you know your meter is

accurate? And in this little article, it says that they are now required to an international standard of within 20 percent margin of error and every time you open a box of strips that you should check with control solution. But, as I said, $15 for control solution that's going to expire in 30 days. There's a disincentive to buy it on your own. That's why I would advocate that it goes in the box. But they do manage to name the criteria to choose from to compare meter name, the blood sample size, what kind of battery, etc. But there's absolutely nothing that compares accuracy. And there is no way for an informed consumer today to determine how accurate their meter is. And we even heard that FDA doesn't permit them to make claims because as long as it's within the standard, that's the criteria they have to meet. But I think, as a consumer, I want to be able to compare from one meter to another and simple control solution is not going to tell me that my meter is more accurate than someone else's. So my feeling is there should be standards for comparison, especially for accuracy. People have perceived that they're accurate. A lot of

people if you just ask -- I ask my mother, she's 82. She thought it was within two percent. Surely, if FDA approves it, it must be an accurate meter. And I think that's probably your very typical Type II older population who believes our government cares about it - - and I do believe FDA cares -- but I think that we just don't know what the laws are and what the rules are. Co-pay is another thing people consider. How much am I going to have to pay? Some insurance companies are saying, Well, you can have any meter that you want, but for this meter, you're only going to have a $10 co-pay. For the other, you're going to have a $50 co-pay. Well, when you're testing 12 times a day, it's going to make a big difference. Other things that people decide, How can I get a free one? They're everywhere. Medicaid and some insurance do not give any options whatsoever. This is the meter you're getting; this is the meter you're going to use. Take it or leave it, or buy your own. And then no insurance people -- they're going for the cheapest strips. So here's one -- this person actually lives in my area. He says, I'm a little worried about this

meter. I'm not going to mention it. It's not working properly. I don't have control solution. I need to go get a free meter somewhere, because he's looking for yet another free meter. It's a problem. Other things that they do to choose meters -- obviously, if you're physically challenged, it has to be an ease of use -- how to get the strips from the container out of the container. Sometimes they open the container, all the strips fall on the floor because for whatever reason it was so hard to open that container, it snaps and it falls down. How to get the strips into the meter, getting the blood onto the strip, large display backlight and, of course, for visually impaired, they need a voice activated, so these are other considerations that people take into account when choosing a meter. So when asked where do you obtain the glucose meter most frequently used in your home, almost 30 percent from healthcare provider. And this was interesting, almost 30 percent from your insulin pump company. And 22 percent from your local pharmacy, and then free or your DME company, etc. The insulin pump and CGM users don't really choose which

meter they want -- they need to use the meter that's going to beam up the information either into their pump or the specific one that's going to calibrate their CGM, and that's what they're using. And all -- of course it's not approved by F -- it's not approved, it's not indicated, but I can tell you that dose decisions are being made by CGM users and they are calibrating with the meters that in my opinion are not sufficiently accurate today. When asked to rank what are the most important factors -- I had listed maybe 15 or 20 -- I will give Arleen a copy of the survey. What are the most important factors when choosing a meter? Number one was accuracy -- 77.5 percent. Number two -- blood sample size, three -- cost of test strips. They could rank all of the different things as either most important, important, least important, not applicable. Perceived accuracy -- so I asked -- and this was not a well-worded question. I now understand better that the less than 75 has to have a different parameter. So I said according to FDA requirements, home blood glucose meters must be within what percent of actual blood glucose value from a lab,

and if you're unsure, please choose your best guess. And to me it was surprising -- 46.1 percent believed current accuracy required is between one and ten percent. And then you've got, you know, you're more knowledgeable people that said 20 percent because they knew and then a little over five percent, six percent said higher. And so I'm here really representing all of the people out there, and it's a daunting task, that use home blood glucose meters every day. Numerous times a day, their lives depend upon it. They're making dose decisions for insulin for themselves, for their children. Here's some quotes, "I'd love to find a meter that had closer error tolerances -- accuracy less than one to two percent." This person says, "As everyone knows, meters are allowed to be twenty percent off. It's unacceptable. I have four meters lined up to do a test using the same blood drop. Each meter shows a different number -- 80, 90, 100, 110. That could still be a range of blood sugars from 60 to 120, so which number is it? And if anything needs to change, it's the accuracy of the meter." And then this person asked, "What does a

person with Type I diabetes do when they have no faith in their glucose meter?" And it's tough -- it's tough when you can't afford to buy another test strip. You can't afford to repeat the test. You know that you don't feel like what it says, but you've got to make a decision. Here's another one, "No way is 20 percent variance good enough. That the FDA does not make the band tighter is being irresponsible for my child's health. We dose based on that number. She's so insulin sensitive; it would make a huge difference to control. They can require meter makers to do better." And another -- they feel that it's appalling and there's no reason why it can't be within one percent. Well, I'm not an engineer, I'm not industry, I'm not here to say what can and cannot be achieved. I'm just here to share what people feel. So regarding yesterday's discussion. Consumers are the end user, regardless of the setting. Hospital, office, school, soccer field, home, nursing homes, daycare -- we're all the end users. Yes, we need accuracy in the hospital to protect people from hypoglycemia. We need the same thing at home. It's really not that much

different. When meters are even more off in the high end, we're giving extra insulin that should not be dosed. But we're basing it on these meters that do have that error. Labeling -- we have no way as a consumer to know what accuracy there is in any meter that we choose. We need to have 1) education and 2) labeling. We need to know how we can make an informed decision. Shipping and storage -- in my opinion, there should be guidelines as far as that goes. We don't know how long they're sitting in the heat, we don't know what they're exposed to, and it's most likely that people are not going to be using the control solution every time. Tight glycemic control -- I can tell you from a parent's perspective, they are always trying to get it to 80 to 120. It's almost an obsession -- parents sometimes check blood sugar two times in the night, in addition to all the times during the day. It is considered best practices. Women who are pregnant have an extremely tight control. And for them to be off, it's even more dangerous. And the outliers do happen, and each outlier is a potential disaster. At least for a

little child and for anyone taking insulin, if they are not going to recheck, or double check, or triple check. So the outliers cannot be dismissed. Usability and convenience -- it just absolutely cannot trump accuracy. Accuracy has got to be primary, it has to be paramount. It must be improved. Regarding the suggestion that there should be different meters for Type IIs on oral medication versus Type II on insulin versus Type I who's on insulin, I think in theory it really does make interesting and good sense. However, in reality -- well, actually I think everybody deserves accuracy. But in reality, what's going to happen is managed care is going to give people the least accurate, the cheapest meter available. And that's what's going to happen regardless of the indication. I also don't think that anybody should have to have less -- why should anyone be exposed to less accuracy? Why should anyone be exposed to possibility making a dose that would be wrong, even if it's oral medication? And I feel very strongly -- we have to phase out the inaccurate lower standards. People can and will learn to use new meters. People

can and do learn new technology every single day. I thought that Marc's graph -- ten percent was absolutely compelling. The difference between ten percent and 15 percent, or the difference between ten percent and 20 percent was extraordinary. And even between ten and 15 percent was huge. So my feeling is if there are meters capable of achieving accuracy within ten percent today, that should become the new standard. And on behalf of all patients who depend on blood glucose meters, I thank you. I thank you for thinking of them as human beings, not just people that -- not just a number in a study, not just a number and how many strips you can sell. These are human beings. And I did have a video but it won't play, of an adorable three year old testing her own blood sugar. She checks, and then she doesn't get enough blood. And then she checks again and she has two little holes. And then she puts the blood on the strip and then the meter slips out of her hand, but she's so proud of herself because she's done it herself. And these are the people who are testing every day.

DR. HARPER: Thank you, Ellen. That was

very compelling, and we have time for a few questions for you.

MS. ULLMAN: Thanks.

MS. PINKOS: You said two things that I'm interested in hearing your opinion on. One, that people do -- are interested in the accuracy of the meter. Do you have any ideas on how would be an effective way of giving that information to consumers so they would have the information available to make an informed decision? And maybe even it might be something for physicians. And the als -- the other thing is do you have any ideas on what is an effective way of communicating the limitations of meters to home users?

MS. ULLMAN: Oh, okay. The first question. Well, certainly I would love for ADA to include it in their annual consumer report of comparisons so that people could actually compare and there -- and this is something that people likely do refer to, at least once a year. And why -- on the box. I think we have to set standards so at least we have comparison standards and Dr. Ginsberg, you certainly showed how

we can put it right there on the box, on the vial. And I'm sorry, the other question?

MS. PINKOS: What's a good way of communicating the limitations to users? We kind of heard that people aren't aware of the limitations. Is there any ideas you have?

MS. ULLMAN: Certainly not in the microscopic font in the patient inserts. I think it has to be in any user quick reference guide -- large, colorful. On the box, of course, do not use if you're anemic. You have to use terms that people will be familiar with. They're not going to know their hematocrit level. But there are people out there anemic. Ten percent of the people with Type I diabetes -- up to ten percent have celiac. A lot of those people are anemic too -- many of them are undiagnosed with celiac, so we need to use terminology. The other thing that would be really great if we could register each meter, so that when there's a recall, people get an instant e-mail notice.

MR. MELKER: Rich Melker from the University of Florida. First of all, thank you for grounding us

back down to the reality of what the people in the real world have to deal with. I mentioned glucose control solutions yesterday. I did a survey several years ago of some of the major pharmaceutical chains -- - pharmacy chains, excuse me. And one chain sold 300,000 glucose meters in a year and less than two dozen vials of control solution. So most diabetics have no idea what to do with glucose control solutions, and as you know the manufacturers went from having a high and a low to have a normal and they don't even include it sometimes anymore. The answer to that issue is very simple. The manufacturers have to figure out a way of, when you put a strip in a meter, if the strip isn't good the meter doesn't use it. There is no way that the average diabetic is going to understand how to use glucose control solutions. The big problem is when somebody leaves their meter in a car in Florida in the summertime. They've probably ruined all the strips and they're going to get wrong information from those strips if they use them, but you have the situation where, unlike me where I do a lot of research and I get a lot

of free strips and I can stick myself four or five times and look at different meters and look at multiple strips, the average person has a vial which they left in the car and they're on the second strip and the strips are no good. To throw away 48, 47 more strips is a huge problem for them because they are not going to get anymore unless they pay for them out of pocket, and just to ground people in reality, the major manufacturers have all kept the price of their strips to the very same price and on average, they're about 75 cents a strip. So, the other last thing I want to say is they talk about strips only using 0.3 microliters of a sample, but if you have a little drop of blood on your finger, and you don't line it up just right, you just wasted a strip. So it may be .3 microliters that it takes to do the sample, but if you don't get a nice drop of blood on your finger, you got about a 50/50 change of that ever going into the strips. I've also encountered several instances where you open a vial and no matter what you do, the strips don't actually -- the capillary action or the lateral flow, whatever you call it, doesn't actually pull the

blood into the strips. And since I understand how the strips work, I'll go and take out my loop and I'll look at the strips and find out that the little hole that is supposed to be there that allows the air to escape when the blood goes in wasn't punched in the right place. So, you've got a lot of strips, a lot -- L-O-T -- meaning a whole lot of strips that the company probably made wherein the manufacturing process, they missed the spot. And I can tell you over the last 15 years of testing five to seven times a day at least, I've encountered this problem on numerous occasions. I've also encountered the outlier situation on numerous occasions, where one strip in a whole vial is completely different than the other ones. Because I'll go take a couple more strips, and then I'll take some strips from a new vial to test them against those. The other thing that nobody has mentioned here is that most -- well, I shouldn't say most -- a lot of diabetics have more than one meter. They keep one at home and they keep one when they travel. When I travel, I always take two, just in case I have a problem with one or it decides to

finally fail -- which they do. So, unless they're using all the strips frequently for both of those meters, some of those strips are going to become outdated. These are the realities -- the real things that people that have diabetes deal with everyday. It's really nice -- and I'm from an academic medical center, for the academicians to come up here and talk about how in very controlled environments what they're capable of doing. Most diabetics -- first of all, I'll just give one last anecdote -- I walk into my hospital as a patient and I'm on a surgery service and they tell me their putting me on a sliding scale, so I sit the surgical resident down and I explain to him about Lantus and Humalog and I'm going to test my own glucose and I'm going to give myself my own insulin unless they get somebody on the floor who understands how to do it. I call my diabetes colleagues, they come on the floor and they educate the surgeons for my benefit, and the day I leave, it never gets done again. So, the reality is we have all kinds -- we have 5,000 hospitals in the United States. Most of them do not do anything that you've heard today.

They're completely different. They're using sliding scales, they can't test once an hour, I can go on and on and on. They don't even know how to calibrate the meters that they have on the floors. We've published some data on the effects of temperature and humidity and these are the real world issues and these are why people are overdosing on insulin and getting hypoglycemic or walking around with sugars of 240. That's the reality. It's really nice to hear the other stuff, but glucose control systems have to disappear. The manufacturers have to figure out a way that if as strip is bad, you put it in the meter, and it tells you they're bad, and you can send them back and get new strips if they're fault of the manufacturer.

DR. HARPER: Thank you, we actually --

MS. ULLMAN: So I wanted to ask you --

DR. HARPER: We only have time for one additional brief question. If we could hear from someone, perhaps, that we haven't heard from yet.

MS. LOON: Thank you. Judy Loon --

DR. HARPER: First of all, Ellen, did you

want to respond to that?

MS. ULLMAN: Well, I just wanted to know if when you discovered that the air hole on the other side of the strip was not pierced properly, did you report it to FDA, or did you report it to the manufacturer, or what did you do? Because this is what we need to educate the consumers, too. What do you do when you discover --

DR. HARPER: Yeah, briefly.

MR. MELKER: Real quickly -- I used to report a lot of stuff and it doesn't -- nobody cares. It goes into a database, nobody looks at the database. I stopped doing it. I just take out a new vial of test strips.

DR. HARPER: We actually do care, and when you report through the -- when you report through the website that I gave in my slides, they actually -- we read and we actually contact the reporters as well, because we really do want to understand these issues.

MR. MELKER: [Off mic.]

DR. HARPER: You can report directly to us, actually. I encourage that.

DR. LOON: Judy Loon. I'm from Hilton Head in private practice. I also work with the veterans in Savannah at the outpatient clinic. I think it's good that we hear what patients and caregivers are really thinking about all of this, so that's a nice survey. But again, when you even look at that survey, it -- you know, anyone who responds to a survey is more serious about their diabetes and you said they all have insurance. So I shudder to think what my patients in Savannah look like. But I share his whole thing about the control solution. Because it is a problem. If you look at Medicare, they will only give you one bottle for six months. So he opens the bottle, it's no good after 30 days, so five months they have no control solution. In the VA, we just changed meters and we have trouble enough to try and get the simplest meter and teaching to their level. So they decided, in their wisdom, to take the control solution out because that would be a problem teaching. So they get no control solution. But I think one thing that we haven't talked a lot about these two days is mail order houses. And that is how patients

get a lot of their machines. And there is no education, trust me. They will send the cheapest meter, the cheapest strip, because their mark- up on the cost of the strip -- they want to send you the thing they're going to make the most money with. So the patient gets no education. And they will just call the patients -- they get their names off of rosters, and they will say, "Have you had a meter in three to five years? Well, let's send you one." And they get whatever the company sends. Physicians don't have time to look and see what that is. So that to me is a real concern. And, you know, you're mailing these strips out. Go to a post office in Savannah in the back room. It's as hot as Florida, trust me. So, you know, these strips cannot be good. But this is, in reality, what's happening. And when you try to report anything -- I actually had one of the big companies -- on two patients, they sent, to be signed, strips they'd mailed to two dead patients. And, when I tried to report it to Medicare, I went through five people, and no one cared. So, even when you try to report these errors and things that are happening out

there, you don't get anywhere.

DR. HARPER: We would really like you to report to FDA on that, because we can work with the manufacturers to make sure that those types of complaints are addressed.

DR. LOON: Yeah, and the mail order houses are a real problem, I can assure you right now. I try to get my patients to use reputable ones, if I can find some. Or, you know, we got them into what meter to use. But they really -- the mail order houses do not care what they send out.

DR. HARPER: We also take trade complaints. You know, complaints about companies. But we really appreciate all this feedback, and Ellen, thank you very much for a wonderful talk.

MS. ULLMAN: Thank you.

DR. HARPER: So I'll just stay here now, and introduce our next speaker. Dawn Hanson is from St. Agnes Hospital in Baltimore, and she's going to be talking to us about risk mitigation in hospitals.

MS. HANSON: Good afternoon, everyone. Let's see if I can get the little thing here to work.

. .thanks for the technical help. This is a rendering of what my hospital is going to look like in about a year and a half. We're building a new, 120-bed patient tower. The problem with that is it makes us budget constrained, so as much as I would like to buy new glucose meters right now, it's not going to happen. Maybe once we're closer to having the tower finished. I'd like to thank the FDA today for holding these meetings. We've had a lot of interesting discussion and I've learned a lot, and I'm going to try to take as much of it back to my hospital as I can. St. Agnes Hospital's been around since 1862. Our current building is about 50 years old. We're about 15 minutes from John's Hopkins and the University of Maryland. Our emergency room sees 86,000 visits a year. We trade off with another hospital as being the first busiest ED in the area. We have 23,000 admissions a year, about. So we're -- they don't like me to say, We're a community hospital. They like me to say, We're a teaching hospital, which we are. I don't know what's become the problem with saying community anymore, but I guess the trend in

public relations and marketing is to stay away from community. The other thing that the FDA folks wanted me to let you know is that we do use the Sure Step Flex glucose meters. The talk today is going to be on risk mitigation, which we've already been introduced, and we want to talk about what steps we take to control or prevent a hazard from causing harm and to reduce risk to a tolerable or acceptable level. The key to that, for me, is the acceptable level. We've had a lot of discussion over the last two days about 20 percent, 15 percent, ten percent. I know 20 percent is too much. I don't know if we can get down to 10. To accomplish that, what do we do in the hospital? We have to establish appropriate measures, processes. Part of that is training. Another key is what's practical? What can we afford to do? Part of our risk mitigation framework is we have to follow the Joint Commission standards. We have, in a lot of organizations, point of care testing committees. We have a point of care testing policy that covers all of the expectations that we as a laboratory and nursing have to take care of issues such as glucose meters

that aren't working properly, or new areas that want to put glucose meters in place. This year, we found out that our dialysis center was using a home meter. Our dialysis center is contracted out, so we never really went in there, we didn't know what was going on. But we did a Joint Commission mach-inspection in there and found out that they had three different meters, all different companies. So, we replaced that with a hospital meter and now I have to learn a lot more about the dialysis center. Part of our risk mitigation framework is our computer equipment and the meter software that goes with it, middleware, meters with lockouts, QC and proficiency testing. I'm also going to cover a little bit more with the documentation. Occurrence management, which I don't think anybody really touched on except when one of the docs that talked about his duplicate glucose checks that they originally used for billing. We also use our hospital education department very heavily to help us with a lot of our issues. Joint Commission accreditation standards -- for all of you out there, we've heard a lot of talk about POCT-12 for the CLSI,

we've heard about the ISO 15197 -- did I get the numbers right? We leave and die by the Joint Commission accreditation standards. We're also CAP accredited, but CAP has kind of muddied out the wave testing standards to the point where we almost don't have to be too concerned about them anymore. Our bigger concern is the Joint Commission accreditation standards. They are required to have a Medical Director -- he's supposed to be required -- he's supposed to be responsible. I heard the doctor get up and talk about the different meters that he has used. It'd be -- I'd be really surprised if most the doctors, including my Medical Director, actually knew what brand we used or how it worked. That's not a criticism for him -- he's very busy, he's doing search path and pros and sections, but that's not his area of expertise. For our operator training and competency, one of the new standards for Joint Commission is licensed, independent practitioners. Licensed, independent practitioners are physicians, physician assistants, nursing practitioners, certified nursing anesthetists, and now all of a sudden, we have to

train them for working on any instrument that they perform testing on. And I talked to a lot of people in other hospitals, and they're like, "Well, we don't have doctors that do testing." You'd be surprised what you have out there and who's doing that testing. We recently just trained all of our anesthetists and certified nurse anesthetists. The reason we did that is because we finally got our standards, and we're in our Joint Commission window. So we had to do this big training push, and of course, what we're going to have to do is do that every year. Doctors are particularly hard to get a hold of, and in general, I don't really think they like to be told that they have to be trained on something. And they really don't like it when you tell them that they can't perform testing anymore because they didn't do hands-on competency. Ellen talked a little bit about the package inserts. I totally agree with everything she says about the package inserts. My package insert for LifeScan is like this big and that long. And I read it because I have to, and I read it every time we get a new lot number of glucose meters. I keep looking for things

to change. Sometimes they do. And then I have to deal with getting that information out to a group of people who typically are the nurses. The problem is that the nurses are not the ones that are doing the majority of the testing. It is our patient care technicians and our nursing assistants. The next piece of our framework that we work from is a point of care testing committee or a policy. A committee is great if you can get the people to show up. We tried to establish point of care testing committee -- didn't work out so well for us. What we went to was a hospital-wide policy that gets reviewed every year by me. The Joint Commission requires that all your policies actually get reviewed every three years. We review ours every year. But it is a hospital-wide policy, and it goes through every single responsible group of people and tells exactly what we -- I -- expect them to do. So, I even go to the point -- I list the lab and what we're supposed to do, and then what nursing's supposed to do, what bio-medical education -- or biomedical engineering is supposed to do, hospital education, information systems. We're, as the laboratory in

charge of this testing, and we can't do the whole job by ourselves, but unless you tell people what you need them to do, they're not going to pick-up and offer -- everybody is just too busy. Computer equipment -- our venders tend to give us the minimum requirements necessary. What you see up there is my favorite configuration for my hardware for my LifeScan software to sit on, and right now I have a RAID 1, which is two hard drives, so if one dies the other one picks up. The RAID 3 is better, that's where I'm going next time, and the server operating system. The reason I have this up here is, once you start producing glucose results that get sent to your EMR -- and they're immediately available. We have wireless connection, albeit some manual wireless connection. They want their results and they want them now. So if your hard drive goes down and you only have one, you're out of luck. And there's nothing worse than getting the phone calls from administration because doctors are complaining because they don't have their results and the nurses are having problems doing insulin. So, I recommend anybody to have at least two, if not three,

hard drives on their system that handles their database software, which is what we're going to call here the manufacturer's software. It has a patient result repository. It also does operation certification tracking and QC tracking reports. The patient result repository is especially important to us, especially Joint Commission, because Joint Commission requires us to track the patient, the results -- which we do in the EMR. It also requires us to keep track of what meter that test was performed on, what lot number the strips were, and was the QC performed, and what was the lot number of the QC? This data repository is the only way we can do that, because we can't transmit all the information across to the EMR. The other nice thing it does is it keeps track of our operators. It would be really nice if, in newer software -- and mine's pretty old at this point, we would be able to have the ability to actually send out an e-mail notification to those folks that are coming up on certification. There's probably two to three phone calls a day that we get from somebody saying, "I'm trying to run a glucose and

I can't run a glucose. The meter won't let me run it." Well, that's wonderful, but meantime, we've got a patient they're trying to perform a test on. That's delayed; they have to get somebody else to run the test because we've locked them out. Our operators use a barcode on their I.D. badge and they have to scan that I.D. before the scan the patient I.D. armband before they run a test. So, if they can't do the testing because they haven't done their certification competency, which we require QC every six months -- some people require them also to do patient testing -- but we have people that actually don't do testing that frequently, so we try to stick with the QC. The QC tracking reports we pull monthly, and this is part of what we do with some of our auditing, and I'm going to talk about that a little bit more when I get down to our occurrence reports. Our software goes from the database software, to middleware, to our lab information system, to the EMR. We pull audit reports, which are patients with duplicate tests, patients with critical results, and patients with results that are zero or greater than 500. Another part of our

framework is our documentation. We have a quality plan, procedures, procedure notes, package inserts, training scripts, training checklists, competency quizzes, and our implementation documents. Oh, she's giving me the five minutes and I've got like a zillion slides to go. The important thing to note here is procedure notes. My procedure for my glucose meter testing system is like 18 pages long because of all the stuff that's required to be in it. Procedure notes are like job aides, quick reference cards. It just has the information on it to get the job done, which leaves out a lot of important information that we just don't have time to get them to read through. We tell them, but they don't retain that much. Occurrence management -- this is where we go back to those reports with duplicate test outliers. Originally we started pulling this report because we charge for our glucoses and it picks up any patient that's had two glucoses within 10 minutes. At 15 minutes, that's where our protocol says if you have a low glucose, you get your insulin, and they repeat it in 15 minutes. So we're looking at anything that's less than 15

minutes -- we set it at 10 -- we get results that are really close, we get the 124, 130. They ran the test, they had a bad feeling, didn't match patient condition, they ran it again, but it was okay. Then we get the 124, 240 -- wasn't okay. What we do -- and this is the same with everything else on the slide -- if they don't have a comment with a critical result, or they have a zero, or they have a greater than 500 and they didn't send a specimen to the lab, unacceptable QC, or equipment issues, we create a report, it goes to the nursing unit, we have a contact, or it's usually the team leader on the nursing unit, and she's required to follow-up with that person to find out what went wrong, if they knew what went wrong, or why they repeated the test. Or why they didn't put a comment in. Or how they got a zero result. When we first started with the system, we would hold up the duplicate. We would hold the second result. What we came to think about about six months into that is, "Did we hold the right result out of the EMR? Is that the result they treated on?" We had no way of knowing that. So what we started doing

is just releasing all those results -- they're already making that decision on the nursing unit, so why would we hold that result. But when we got the system, that was sort of the recommendation, "Well, you can hold the second result." Yeah, but that's probably the one that they're treating on because that's the second one that they ran. So we no longer do that, however, when we do duplicates, we do credit the patient for the second result -- or the third result, because sometimes two out of three is better. A hospital education -- our hospital education department trains all new employees. My next thing is to get them to train the doctors. They train them on the glucose meter use, hyperglycemia, hypoglycemia policies, and not too much more than that. We train a lot of people every month because staff turns over quite frequently and I can tell you that they don't use the package inserts to train. They also assist with our annual competencies. We do on-line quizzes. We have competency days for instruments because typically they have to have some kind of hands-on training. The meters -- when we get new meters, we validate them

before patient use. We do linearity studies. We do the five levels four times. We run it through the software that the vendor gives us to determine whether the instrument is appropriate to send out, we do QC in duplicate. Typically the meters are good. Probably in the last ten years, I've only had to send one back that didn't meet standards. Infection control -- we have a lot of isolation patients. Over the last two years because of our MRSA surveillance, one of the interesting things that happened to us when we stared this whole hand hygiene, put all the gel out there, put the bleach wipes out there. The first week we lost four meters in our intensive care unit because they got them so wet with the bleach wipes that it just seeped right into the meters and they had to get new meters. We had to send them all back. Sorry, LifeScan. We didn't tell them that was what happened, but I'm sure they figured it out. Amy doesn't care. The other problem that we have is just in general, the precautions all over the nursing units. You can go to any one of our nursing units and they have a white film all over them. And hopefully this isn't causing

any other interfering substances -- or interferences with our glucose results. Strips and controls -- we get large quantities every order. We have to do lot to lot comparisons on those and on our QC. Our users, our physicians, physician assistants, nurses, patient care technicians -- I can tell you in my hospital and probably anybody else that has patient care technicians, which are nursing assistants, nursing technicians, they do 80 percent of the testing, including in the intensive care unit. Now in our intensive care unit, if the patient's on insulin drip, insulin I.V. which is what they call it in our hospital -- they don't go as far as tight glycemic control. The nurses are doing the testing during that instance, but during the rest of the time, it's patient care technicians. Our glucoses, in addition to all the normal places, are used in our labor and delivery suite, on babies that are 15, 20 minutes old. Where are those standards? They're used in the O.R. Not quite -- I'm sure they're testing for glucose, but I don't know under what circumstances. And the one that I love is they do glucoses on patients that are

being recusced. If anybody out there can tell me why they do that, I'd appreciate it. So, I'm just going to flip through these real quick, because these are the things that I wish I had. We talked about standardized meters, smarter software, smarter meters, and I would like -- and we talked about this with Ellen -- I would like when you open the bottle of QC that maybe the cap would change color when it expired, or something similar to that. The other thing that I would like to see are strips that are individually packaged with bar code numbers on them, because then I don't have to worry about how long the bottle was open. And lastly, I think we've talked about this a lot, no result is better than the wrong result. And I learned that a long time ago when I started working in the laboratory, and I would like to not get a result when there is something wrong with that strip. Thank you.

DR. HARPER: Thank you, Dawn. That was great. I learned a lot about risk mitigation in the hospitals and a lot of things that I didn't realize. So before I introduce Dr. Klunoff who's going to give

a good summary of the meeting, I'd first like to thank a few of the people who, without them, this meeting wouldn't have happened: Arleen Pinkos, Katy Serrano (ph), Leslie Landry, and all the people that you saw outside. They did a lot of work and worked for months in order to bring this wonderful program to you, so please join me in thanking them. They did a lot of hard work for this. So now I'd like to introduce Dr. David Klunoff. Dr. Klunoff is a Clinical Professor of Medicine at U.C. San Franciso and the Medical Director of the Dorothy L.

and James E. Frank Diabetes Research Institute of the Mills Peninsula Health Services in San Mateo, California. Welcome, David.

DR. HARPER: Thank you, Courtney. This has been a really interesting meeting for me. I'm going to start by disclosure. I'm a consultant with Bayer, C-8 (ph), Insuline (ph), LifeScan, Madingo (ph), and Rausch. Now, I have an announcement about slides for this meeting. The organization that I'm President of -- a non-profit organization, Diabetes Technology Society -- will post slides of any of the

speakers from this meeting and the mechanism is to get them to Arleen Pinkos, and then she'll get them to Diabetes Technology Society and she'll notify you of the website. Okay. This meeting today has been focused on regulatory standards, and the point I made yesterday was regulatory standards represent what is achievable given the technology and the economic resources that we have. It's a -- there are a lot of things that we like, but the technology or economic resources may not be there yet. Clinical standards are what is desirable, and we've certainly heard some really nice clinical standards today that we would all like to see at some point. What I heard quite a bit of today and yesterday is that there's some idea of having two sets of standards. And there's some precedent for that. For example, if you live in a certain neighborhood, there'll be a speed limit so that you can walk out on your street and not get run over by cars. If you live near a school, there's going to be a slower speed limit. So, we're used to having two speed limits. I mentioned yesterday that if you want to have a building built in California, we

have earthquake standards, but if you want to build a hospital, we have very strict earthquake standards. I could go on with a lot of examples. But my point is that in life, sometimes there is situations where you need accuracy and sometimes you need super-accuracy. So what I'm going to talk about now in the last few minutes of this meeting -- where we go from here, are ten themes which

I believe have emerged from this meeting. So the first theme is that we need separate analytical accuracy standards for different populations -- we need accuracy and we need super-accuracy. And we've talked about who these patient populations are: the ICU patients, the Type Is with tight control -- they need super-accuracy. We also need separate clinical accuracy standards for these two types of populations. And a good way to present this information, I think, that both industry, the FDA, and the academic community can agree on, is with a good error grid. And if there's a good error grid which defines the clinical use and how you're going to make decisions with the information, you start with the error grid

and then the FDA can assign what percentage of the data points have to be in the "A" zone. And the reason is, if you're looking at a scatter of points, they'll ideally be on the equality line that goes at a 45 degree angle, but they're not always on that line. However, if you try to understand why they're not, because there's problems with interfering substances and problems with bias and individual issues, you start getting into arguments about do the interfering substances count, or do they not count. We heard that yesterday. There are a lot of technical questions that are hard for everybody to deal with when you look at these points that are not right on the line. However, if you take these same points and you assign them an A, a B, a C, a D, or E, whatever, and you specify. They just about all have to be in the "A" zone. We know what "A" zone means -- that's the right zone to be in, and then there's no more arguments. We all understand what that means. So I think in terms of clarity, this is something that we can all get behind, and that's what I'm hearing about using error grid for helping to determine treatments, make

decisions. A third theme is that when we look at data, we need to account for certain types of data which are currently not part of the standards. That includes the five percent outliers. People seem really unhappy knowing that these five percent can be so far off, as well as the no report whatsoever and what does that mean? Technically it doesn't count as an inaccurate reading. That's a relatively easy problem to fix and I think that there is impetus at fixing this. Another theme of this meeting I heard was that we should have some new labeling on the product for both analytical and clinical performance. It's pretty clear how this can be done for analytical performance - - there are different numbers that can be chosen. And for clinical performance, it's also pretty easy because you can take the performance on the error grid and simply say what percentage were in the "A" zone or the "B" zone, or the whatever zones you're even allowed based on the FDA ruling. So people want to see labeling, and I think we're going to see more labeling. Now, a fifth theme deals with interfering substances. We know that these are out

there, but different meters test different substances and test them in different ways. So another theme that I've heard is that we should have specific protocols for how to measure these substances. So if we're going to measure for acetaminophen or whatever we're measuring for -- people measure them in a certain way and when you read that this meter is not affected by acetaminophen, you know what it means. And this can be handled by CLSI which has a committee for interfering substances. This could be added on or they could make their own committee. Also, the sixth theme relates to interfering substances is how they're reported. We do not have a standardized mechanism for reporting. This could also be handled by CLSI by setting up a committee on reporting interfering substances. The seventh theme is that since we want more accuracy -- and we have to realize, and I think many people in this room do realize, that accuracy is going to pay -- you have to pay a price. There's a cost for accuracy. The cost could be dollars. The cost could be having to give up some of the features that we like. For example, we might have to give up

on the rapid time that we like, or the drop size, or having no coding features, or stability reagents, or a small number of steps. Possibly tolerance of various interferences, or not having strips with some systems. We're probably going to have to make a sacrifice in some way -- get used to it. And on the same topic, of what we have to get used to, this might also include some kind of sunset laws to take products off the market under defined conditions. And that would have to be discussed. An eighth theme of this meeting is that we need data to address what are the outcomes and what type of performance will generate those outcomes. We heard a landmark report from Marc Breton at this meeting in which he showed what happens to the performance under defined conditions. He picked certain defini -- he defined certain conditions. Again, I would like to see this group write some more articles. It's very difficult to do empiric studies, but at least due some modeling studies, maybe making different assumptions, and let's get a lot of data out there and look at it. Maybe Marc and Boris will even do another paper. But remember, modeling is very

good. It's as good as the assumptions that are made. We need the data to address this important question. Otherwise when we demand greater accuracy how do we know what we're getting and why we're getting it? We need one more data that would request is that we need to develop some processes to improve the performance of the blood glucose monitoring in addition to greater accuracy. There's a sense here -- we all know it. Yes, the meters should be more accurate. But there's more to getting an accurate reading than the quality of the strip in the monitor. These processes involve various types of education. We've heard all of the things that can go wrong where you don't wash your hands, and when you leave the strips out and there are a million things that can go wrong. And we need some education, because we're not going to get there just by squeezing the strip accuracy. That's part of it, but it's definitely not all of it. The last theme is that we need to define optimal targets for glycemic control in various populations. We spend a half a day today discussing what's an optimal target for hospitalized patients who clearly need tight control,

who clearly need accurate meters, but we have to know what these targets are. So I've mentioned ten things. I'm going to wrap this up with what I would say are five conclusions that I have taken away from this meeting. First is that we want better analytical performance. Second, we want better clinical performance. Third, we want better incorporation of factors which will improve performance of blood glucose monitoring above and beyond the meter and strip, analytic and clinical performance. Fourth, we need better labeling and reporting of interfering substances, and fifth, we need better agreement on glycemic targets for hospitalized patients. And, what I continued to notice today as I did yesterday is there has been a very nice atmosphere between the FDA people, the industry people, the academic people, the patients. I sense that we're all in this together; we all want the same kinds of things. I think if we work together, we're going to get there. And since I'm from San Francisco which is the rock-n-roll capitol, I'm going to end with some words from Mick Jaggar from the Rolling Stones, "You can't always get

what you want, and if you try sometime, you find you get what you need." Thank you.

DR. HARPER: Thank you, David. So, now to close the meeting, it's my pleasure to introduce Dr. Alberto Gutierrez, my boss. He's the Director of the Office In Vitro Diagnostic Devices at FDA. So, Alberto.

DR. GUTIERREZ: Thanks, Courtney. I want to actually start by thanking Courtney, and actually the Division of Chemistry and Toxicology who are the people who look after glucose meters. And I do want to thank everybody who came to the meeting, and really let you know that this is an extremely important meeting for us. All the discussion that went in the meeting, not only -- I hope that actually you, as I, was somewhat awed by the complexities of how these meters are used and the landscape of what we're dealing with. And in the Division, we make decisions everyday and we put risks and benefits together. And we make decisions when we see an issue, when we're dealing with a recall, when we're looking at new meters and what their performance is, we make

decisions as to how they're going to affect each and every patient out there. So having a good idea of what the landscape is, knowing how the meters are used, knowing how the clini -- what the clinicians are looking for, knowing what problems the users are finding, are of extreme importance to us. So the meeting -- this meeting has been everything we hope for, and you've helped us make a lot of the decisions that we do every day. I want to particular thank Arleen Pinkos, although I was a little worried when Arleen got up and presented herself as being Arleen Pinkos from Baltimore, that she wasn't quite being honest enough. And anybody who knows Arleen actually knows that her heart doesn't bleed purple. She's a rabid Pittsburgh fan. So I'm not sure about this Baltimore stuff. I also want to thank -- there are a couple -- although Courtney mentioned some people that really put in a lot of work like Katie Serrano and Leslie Landry. There were also some people in the outside that were at the tables that really helped put this meeting together and let me just read a couple nam -- a few of their names like Christine Kellerman

(ph), Eddie Selixon (ph), Susan Monoham (ph), Michelle Garza (ph), Peggy Rooney and Renita Hord (ph). And they really, really did a lot of the leg work for this meeting to be put together. And lastly, I want to thank all the speakers and the panelists, and I want to really thank everybody who made comments because everything that was said is really being taken at heart by us. Thank you very much.

CERTIFICATE OF NOTARY PUBLIC

I, Natasha Kornilova, the officer before whom the foregoing meeting was taken, do hereby certify that the testimony that appears in the foregoing meeting was recorded by me and thereafter reduced to typewriting under my direction; that said meeting is a true record of the testimony given; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this meeting was taken; and further, that I am not a relative or employee of any attorney or counsel employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

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Natatsha Kornilova

Notary Public in and for the

District of Columbia

My commission expires:

April 14, 2012

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